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Synthetic Efforts Towards the Synthesis of Prostaglandin PGF2a

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SYNTHETIC EFFORTS TOWARDS THE SYNTHESIS OF PROSTAGLANDIN $PGF_{2\alpha}$

A Dissertation

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in

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by
Amy Marie Pollard
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OTF, Cinco de Mayo 2013, you are the reason why I do what I do.

-PAP

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LIST OF ABBREVIATIONS

AcCl	Acetyl Chloride
AChE	Acetylcholinesterase
AIBN	Azobisisobutyronitrile
COSY	COrrelation SpectroscopY
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
cPGES	Prostaglandin E Synthase
CSA	Camphorsulfonic Acid
DHA	Docosahexaenoic acid
DMAP	N,N-Dimethylpyridin-4-amine
DTGS	Deuterated-TriGlycine Sulfate
ESI	Electrospray Ionization
ETP	Ethopabate
FTIR	Fourier Transform Infrared
GRAS	Generally Recognized as Safe
GC/MS	Gas Chromatography–Mass Spectrometry
H	Hour

HPLC	High-performance Liquid Chromatography
HSQCDEPT	Heteronuclear Single Quantum Correlation Spectroscopy Distortionless Enhancement of Polarization Transfer
LC	Liquid Chromatography
LHMDS	Lithium bis(trimethylsilyl)amide
NIS	N-Iodosuccinimide
NMR	Nuclear Magnetic Resonance
mPGES-1	Microsomal Prostaglandin E2 Synthase-1
mPGES-2	Microsomal Prostaglandin E2 Synthase-1
PCC	Pyridinium Chlorochromate
PGD_2	Prostaglandin D_2
PGE_2	Prostaglandin E_2
PGF_2	Prostaglandin F_2
PGG_2	Prostaglandin G_2
PGH_2	Prostaglandin H_2
PGI_2	Prostaglandin I_2
PGJ_2	Prostaglandin J_2
Py	Pyridine

Rf	Retardation Factor
ROESY	Rotating-Frame Overhauser SpectroscopY
RT	Room Temperature
SERS	Surface Enhanced Raman Scattering
TNT	Trinitrotoluene
TOF	Time of Flight
p-TSA/TsOH	p-Toluenesulfonic Acid
TXA_2	Thromboxane A_2
TXB_2	Thromboxane B_2

ABSTRACT

This dissertation describes strategies for synthesizing prostaglandin $PGF_{2\alpha}$. Our synthetic design creates the stereochemistry needed for the core and side chains of the target prostaglandin $PGF_{2\alpha}$ and $PGF_{2\alpha}$ synthase selective analogues while incorporating iodocyclization desymmetrization of acyclic dienes. A model system for 4-(iodomethyl)-6-methyl-1,3-dioxan-2-one was developed and synthesized for our target compound 4-(2-(benzyloxy)ethyl)-6-(iodomethyl)-5-vinyl-1,3-dioxan-2-one. Both compounds were successfully synthesized providing useful stereocenters for completing the synthesis of prostaglandin $PGF\alpha_2$ .Efforts toward total stereochemical control of $PGF_{2\alpha}$ include the partial syntheses of bis-diethylanimedimethylsilane and of (4S,5S)-2-((1E,3E)-penta-1,3-dien-1-yl)-4,5-diphenyl-1,3-ditosyl-1,3,2-diazaborolidine.

CHAPTER 1: PROGRESS TOWARDS THE SYNTHESIS OF PROSTAGLANDIN $PGF_{2\alpha}$

1.1 Introduction to Prostaglandins

Essential fatty acids omega-3, omega-6, including eicosapentaenoic and docosahexaenoic acid (DHA), precursors to prostanoids, are critical for circulation, production of hemoglobin, immune function, and anti-inflammatory response.[1] A study reported in 2006 by R. Bayer suggests that omega-3 fatty acids are a possible treatment for inflammatory pain.[2] Studies by Wall *et al.* concluded that increasing consumption of omega-3 fatty acids increases production of inflammation mediators and regulators. [3] Linoleic acid, a C18:2 omega-6 fatty acids (Image 1) is the precursor to arachidonic acid which is oxidized by cyclooxygenase 1 or 2 forming prostaglandin PGG_2, an inflammatory stimulator. In the C18:2 type nomenclature, C18 represents the number of carbons in the chain; the 2 represents the number of alkenes in the chain.

PGG_2 is reduced by PGH_2 synthase forming prostaglandin PGH_2, which undergoes enzymatic reactions to produce five different prostaglandins: PGI_2, $PGF_{1\alpha}$, $PGF_{2\alpha}$, PGE_2, PGD_2, and a thromboxane, TXA_2. The primary prostaglandins undergo additional enzymatic reactions to form additional prostanoids, which are responsible for homeostasis, (Scheme 1).

1.2 Methods of Prostaglandin Synthesis

There are three major prostaglandin synthetic designs. The first is synthesis of the core cyclopentane with appropriate side groups which can be used in subsequent reactions for attachment of α and ω chains.

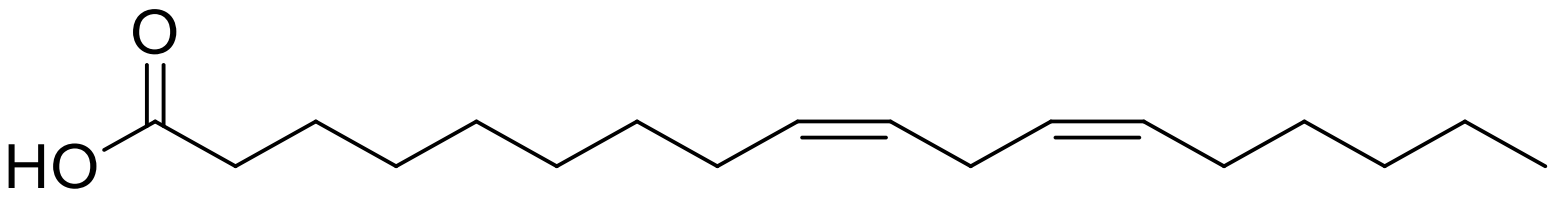
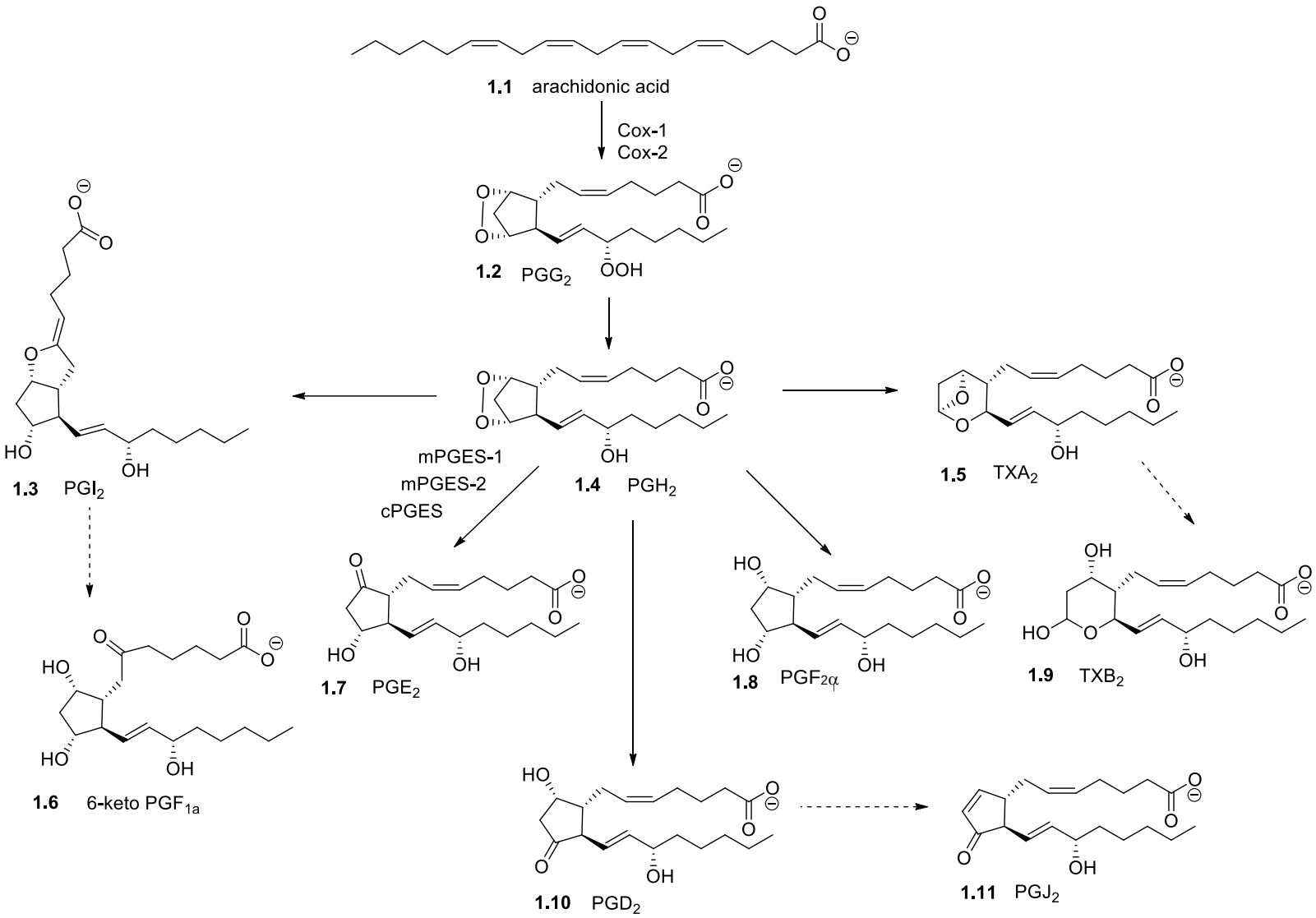


Image 1. Linoleic Acid C18:2, omega-6

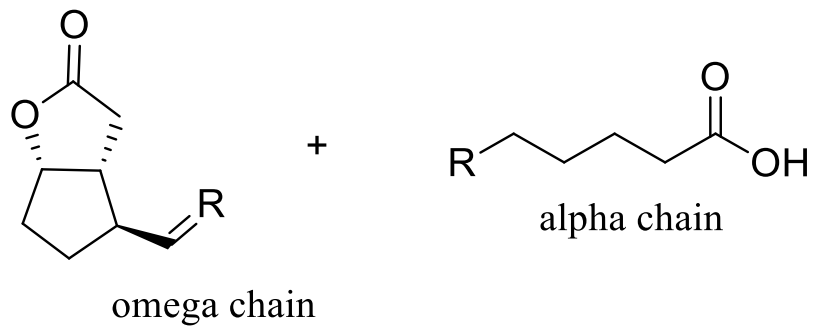


Scheme 1. Enzymatic Cascade Producing Prostaglandins and Thromboxanes

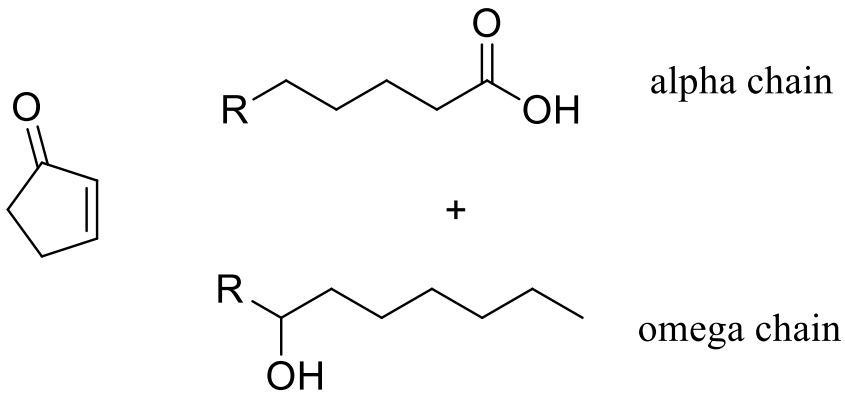
The second is a two molecule coupling, where one molecule contains the cyclopentane core and an attached side chain. This molecule is coupled to a second chain, (Scheme 2). The third method of prostaglandin synthesis is the three component coupling (Scheme 3).[4] Following is an example of each approach.

A derivative of Corey's lactone was synthesized by Augustyns *et al.* in 2005 (Scheme 4). [5] Lactone synthesis began with a Diels-Alder reaction of **1.12** and **1.13**, followed by a radical induced skeletal translocation affording lactone product **1.15**, which was isomerized to produce **1.16.** Decarboxylmethylation with lithium chloride gave lactone **1.17** which was functionalized *via* bromohydrin formation followed by acetylation. Radical debromination of the core structure was accompanied by the potential for side chain attachment **1.19**.

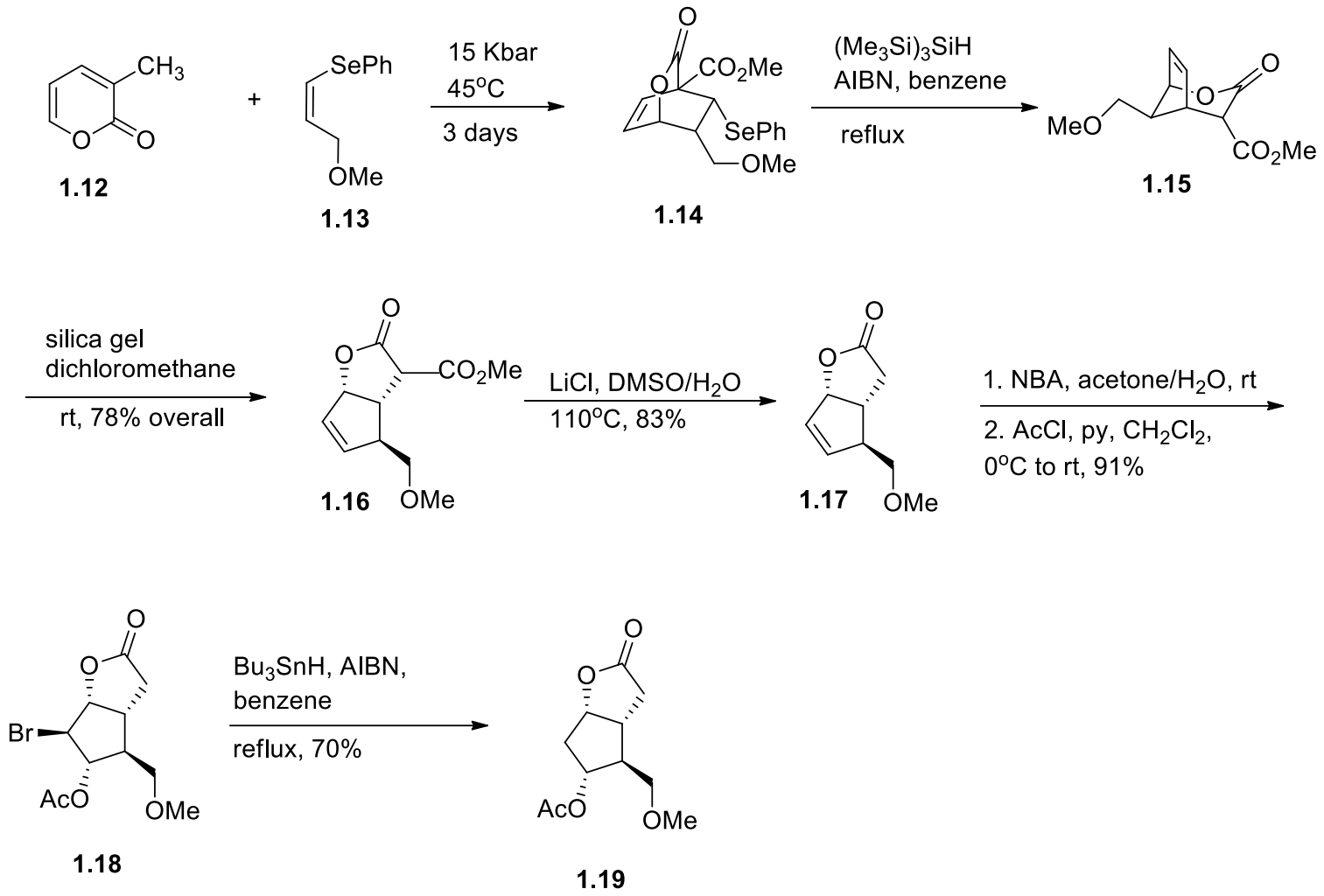
Two molecule coupling completed by Togashi *et al.* [6] commenced with the 1,1-dibromo alkene (**1.20)** coupling to an aldehyde chain affording alkyne **1.21.** Swern oxidation transformed the hydroxyl group to a ketone giving product **1.22.** K-selectride was used to stereoselectively reduce the ketone carbonyl, producing alcohol **1.23.** Reduction of the alkyne, followed by hydroxyl group acylation yielded **1.24**, the precursor to a Pd-catalyzed cyclization, to produce a functionalized core with one side chain attached in an 87:13 R:S ratio at the newly formed stereocenter, (Scheme 5). Scheme 6 shows a one pot, three component coupling method used in prostaglandin synthesis. Cyclopentenone coordinates to aluminum, which stabilizes the position of the enone to allow sequential Michael-aldol reaction of dibenzyl methylmalonate and methyl 7-oxoheptanoate, respectively. Racemic cyclopentenone reacts with an aldehyde in the presence of a chiral aluminum catalyst to yield 75% product yield with 97 % ee.[7]



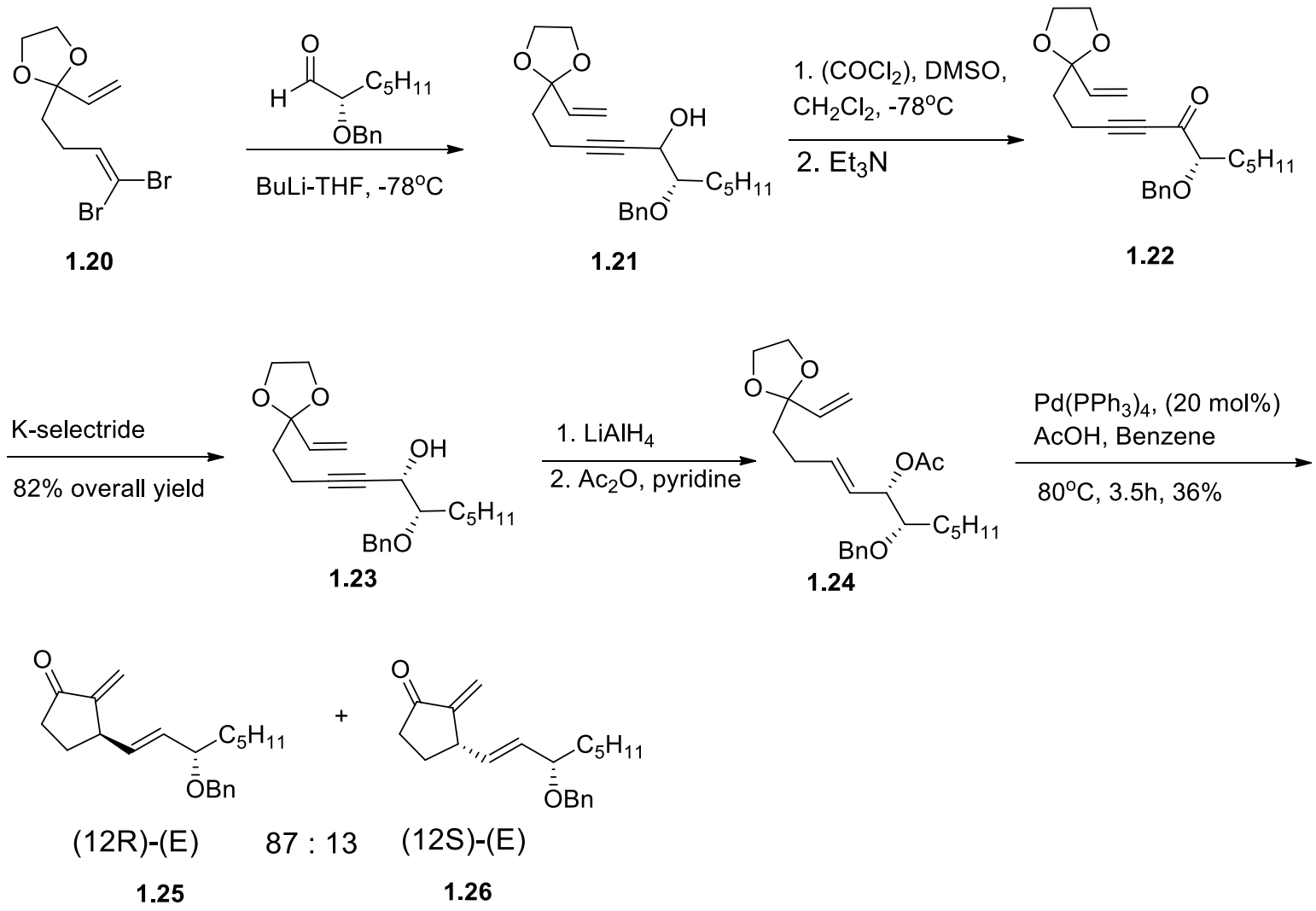
Scheme 2. Two Molecule Coupling Model



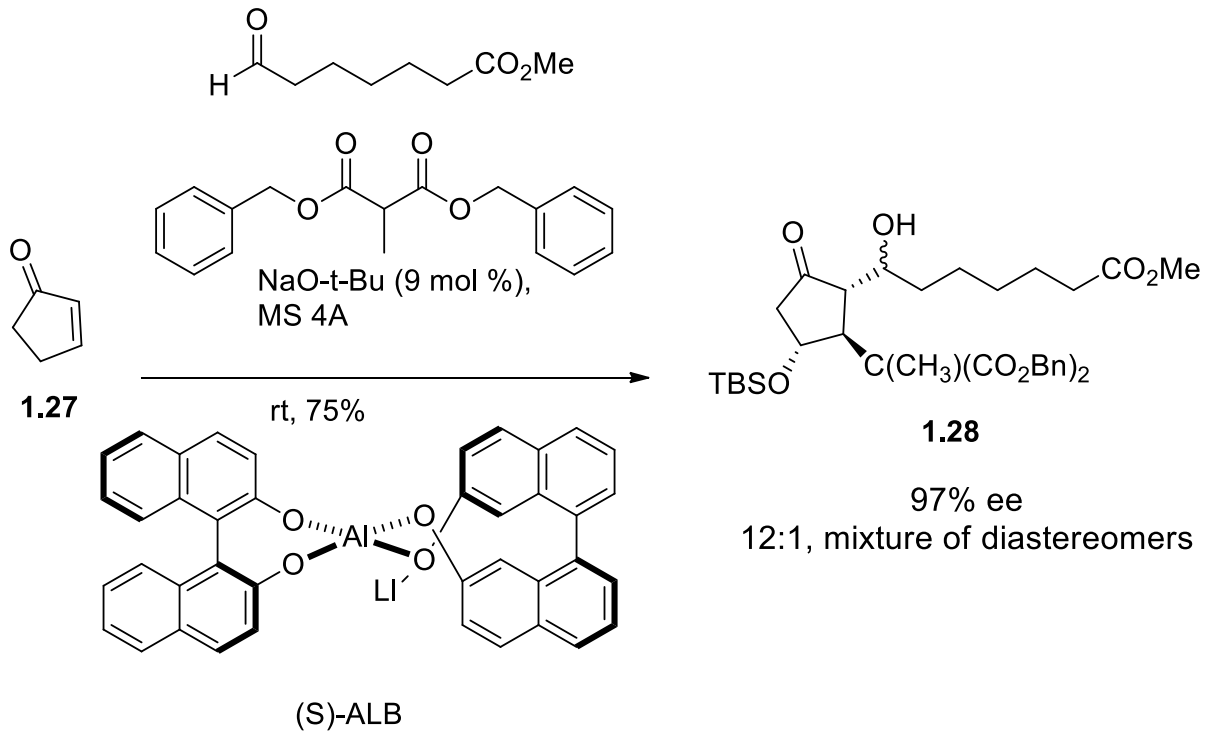
Scheme 3. Three Molecule Coupling Model



Scheme 4. Synthesis of Prostaglandin Core by Using a Diels-Alder Reaction and Radical Induced Skeletal Translocation



Scheme 5. Synthesis of Prostaglandin Core with Side Chain for Use in Two Component Method



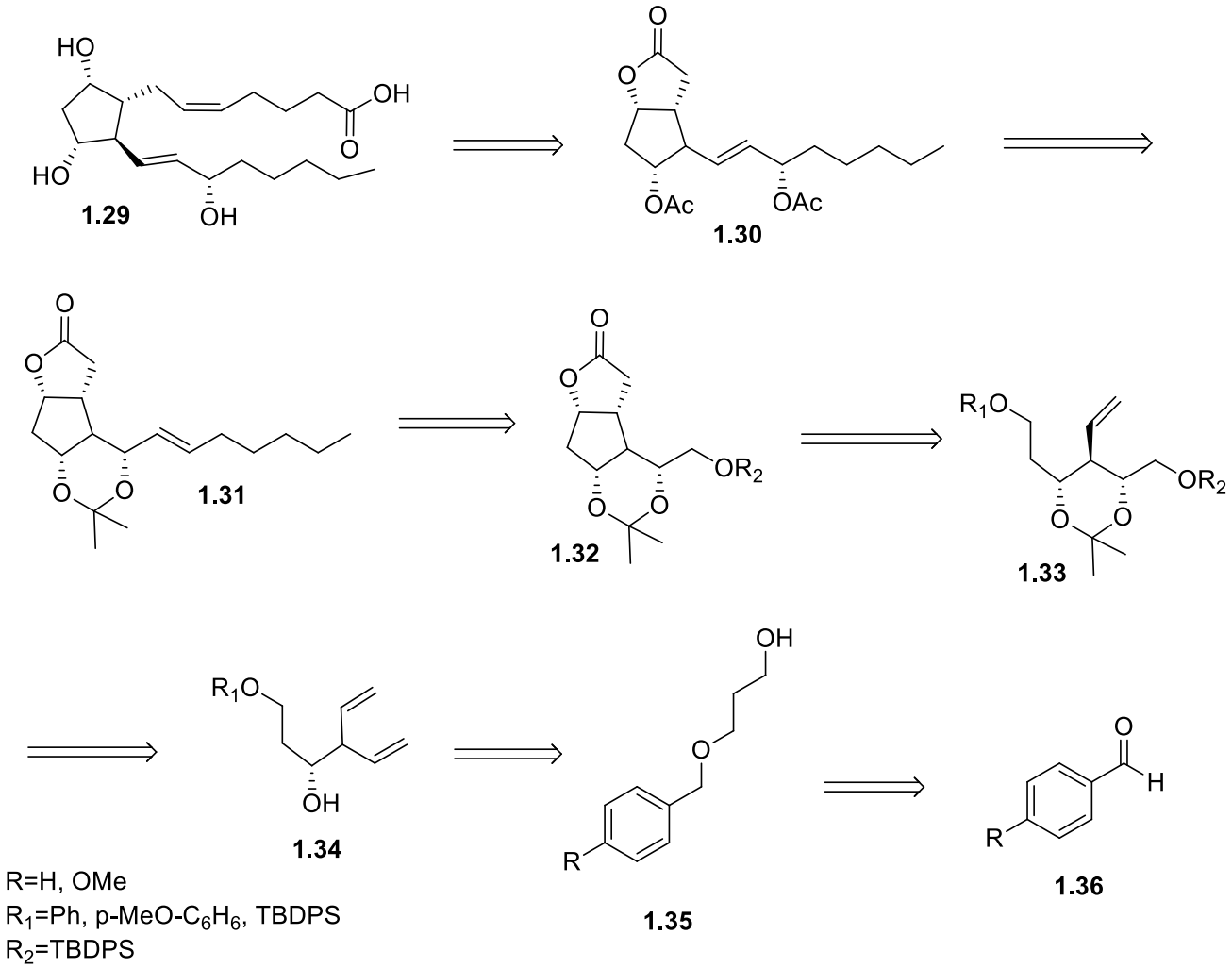
Scheme 6. One Pot Three Component Coupling Using a Chiral Catalyst to Synthesize a Prostaglandin

1.3 Synthetic Design for Prostaglandin Synthesis

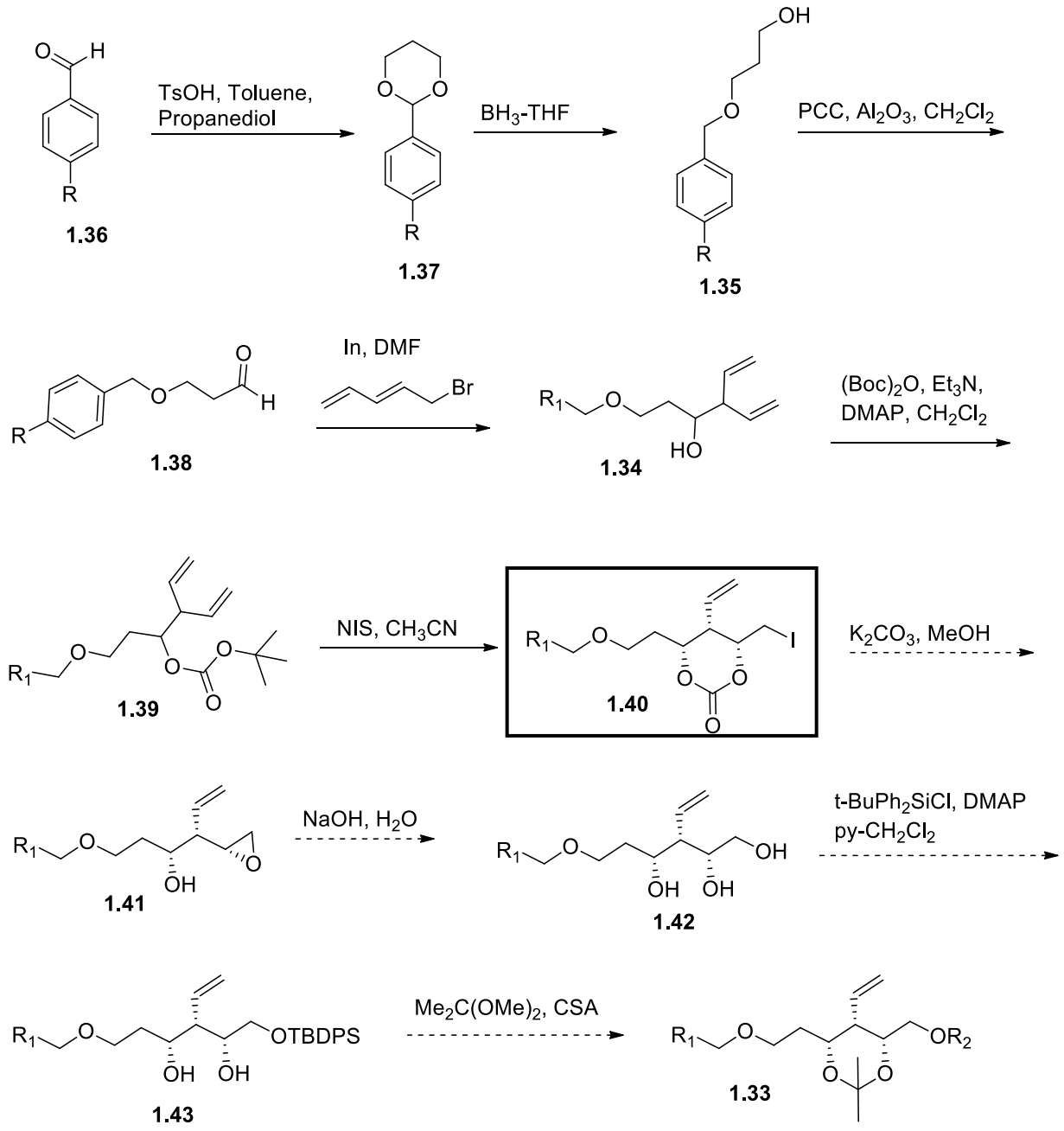
Scheme 7 shows our retrosynthetic design of $PGF_{2\alpha}$. In a forward sense aldehyde **1.36** is transformed to an acetal which is opened via hydroboration, giving alcohol **1.35**. Compound **1.35** would be oxidized, followed by a regioselective pentadienylation to give diene **1.34**. Desymmetrization of **1.34** followed by derivatization gives **1.33.** The hydroxyl group in **1.33** is deprotected, (R_2), and oxidized to an aldehyde. Hetero-Pauson Khand reaction would produce lactone **1.32**. The hydroxyl group in lactone **1.32** is deprotected to give a free hydroxyl group, which is oxidized to an aldehyde and subjected to a Wittig reaction giving lactone **1.31**. **1.31** would then be deprotected and the free hydroxyl groups converted to acetate ester. A [3,3] sigmatropic rearrangement is anticipated to produce **1.30.** Lactone **1.30** is reduced followed by a Wittig reaction to introduce a second side chain, forming **(1.29)** $PGF_{2\alpha}$. The synthesis developed for prostaglandin $PGF_{2}\alpha$ allows us to create all of the stereocenters needed to develop syntheses for PGE, PGD, and analogues. The goal of my project was use iodocyclization in a stereocontrolled synthesis of **1.40** (Scheme 8) with the (S,R,S) stereochemistry at carbons (4, 5, and 6).

1.4 Discussion of Iodocyclization

Iodocyclization is a versatile method for the conversion of an alcohol and an alkene, in a 1,3 relationship, to diols with high stereochemical control of newly formed hydroxyl group relative to the initial hydroxyl group. This transformation was been used in several synthesis of natural products including: Herbarium III, Polyrhacitide B, and Kumar.[8] [9] [10] The hydroxyl group is first transformed to either a carbonate or carbamate then cyclized.



Scheme 7. Retrosynthetic Design of Prostaglandin Synthesis



R_1=Ph, 4-Methoxy-Ph, and TBDPS
R_2=TBDPS

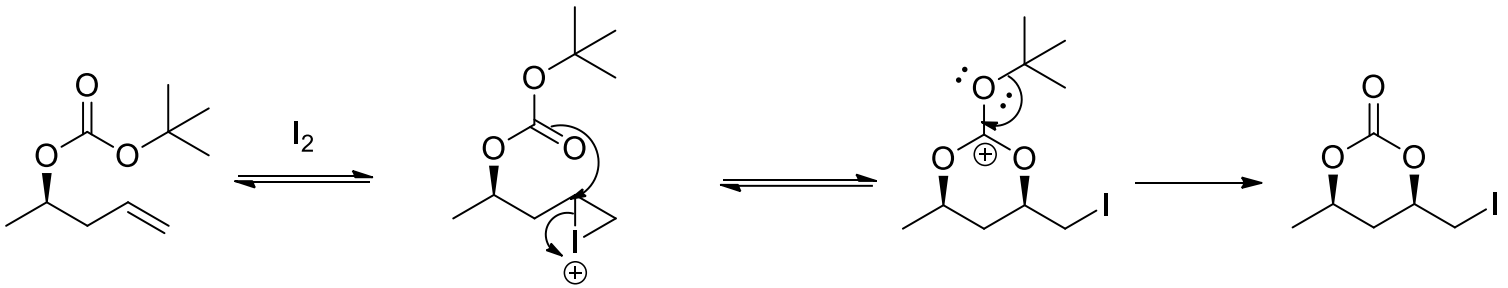
Scheme 8. Route to Alkene 1.33

The mechanism for the diastereoselective electrophilic iodocyclization of a carbonate follows on scheme 9. Selectivity of the reaction is temperature dependent as decreasing temperature increases the selectivity. As the *tert*-butyl group is lost during the cyclization of the molecule, it is trapped by the solvent. By Le Chatelier's principal the reaction is driven forward. In acetonitrile, N-*tert*-butylacetamide (Image 2) is formed during workup. [11]

Friesen *et al.* speculated on the rationale for the stereochemistry in iodocyclizations. Their theory included possible steric interactions the R group and terminal protons on the alkene. However, these interaction are small. An alternative theory involving the S_N2' mechanism was considered and disregarded due to regioselective nature of the reaction on internal alkenes. Barlett reported that chlorinated solvents gave low yields due to inability to trap the *tert*-butyl cation. However, Galeazzi *et al.* reported using dichloromethane at room temperature in the iodocyclization of 3-acylamin esters. The reaction yield range, dependent on substituent, was 75% - 92%. Total diastereoselectivity was confirmed by NMR and GC. [12] Unlike previous syntheses, we will use the iodocyclization to desymmetrize an acyclic dienes and study the stereochemistry of the two newly developed stereocenters. Our study begins with the synthesis of 1-(benzyloxy)-4-vinylhex-5-en-3-ol.

1.5 Synthesis of 1-(benzyloxy)-4-vinylhex-5-en-3-ol and 1-((4-methoxybenzyl)oxy)-4-vinylhex-5-en-3-ol

Dioxanes **1.46** and **1.47** were synthesized in a p-toluenesulfonic acid monohydrate (p-TSA) catalyzed reaction of benzaldehyde (**1.44)** or p-methoxybenzaldehyde (**1.45)**, with propane-1,3-diol. A stoichiometric amount of water was collected to monitor completion of the reaction using a Dean Stark trap.[13] The dioxanes crystallize in ether at -39ºC.



Scheme 9. Iodocyclization Mechanism

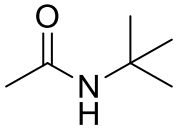
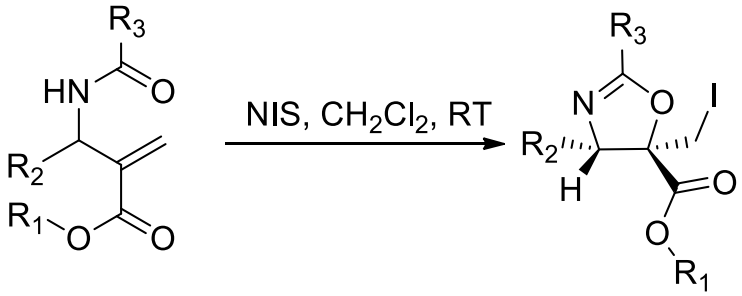


Image 2. N-tert-butylacetamide

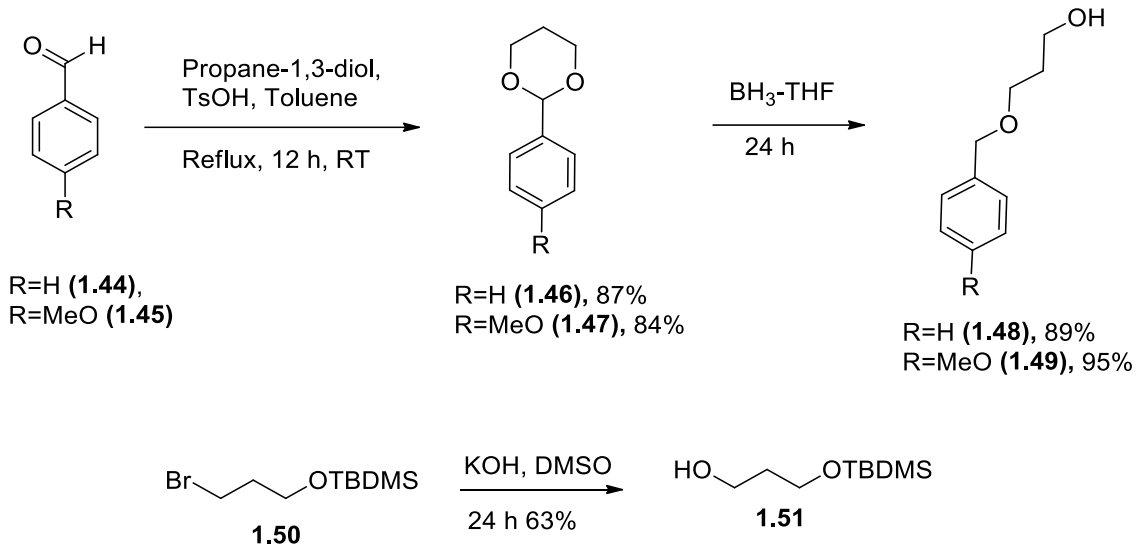


Scheme 10 Iodocyclization of a 3-Acylamino Ester.

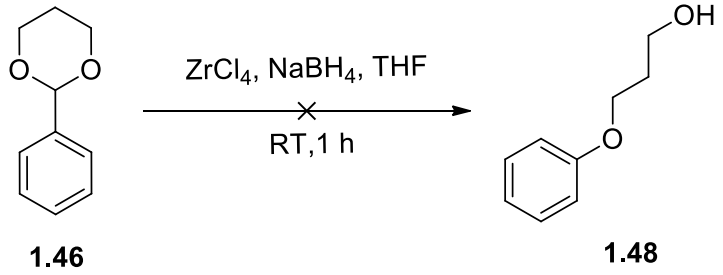
Several rounds of recrystallization removed benzaldehyde impurities, noted by a light yellow color. A borane-mediated reductive opening of the dioxanes forms alcohols **1.48** and **1.49** respectively.[14] The reaction was quenched with methanol at 0ºC under close supervision. A nucleophilic substitution with potassium hydroxide (KOH) was used to displace the bromine on 3-bromopropoxy (*tert*-butyl) dimethylsilane **1.50** with a hydroxyl group, **1.51.** A competing side reaction was cleavage of the *tert*-butyldimethylsilyl group producing 1,3 propanediol, (Scheme 11).[15] The reduction of dioxane **1.46** using $ZrCl_4$ and $NaBH_4$ was attempted as an expeditious alternative to the borane-THF reaction.[16] This reaction was unsuccessful, (Scheme 12).

Alcohols **1.48** and **1.49** were oxidized with pyridinium chlorochromate (PCC) to form aldehydes **1.52** and **1.53** respectively. Chromium by-products aggregated in the flask. A mortar and pestle were used to grind the aggregate and release product. An aluminum oxide addition prevented aggregation without affecting the reaction, which gave the reaction mixture the consistency of coarse sand and a mahogany color. A silica filled medium fritted filter was used. Filtrate had a greenish hue. An alternative oxidation using TEMPO and I_2 was a replacement.[17] The yield was lower than the original method and was therefore not used as a, (Scheme 13).

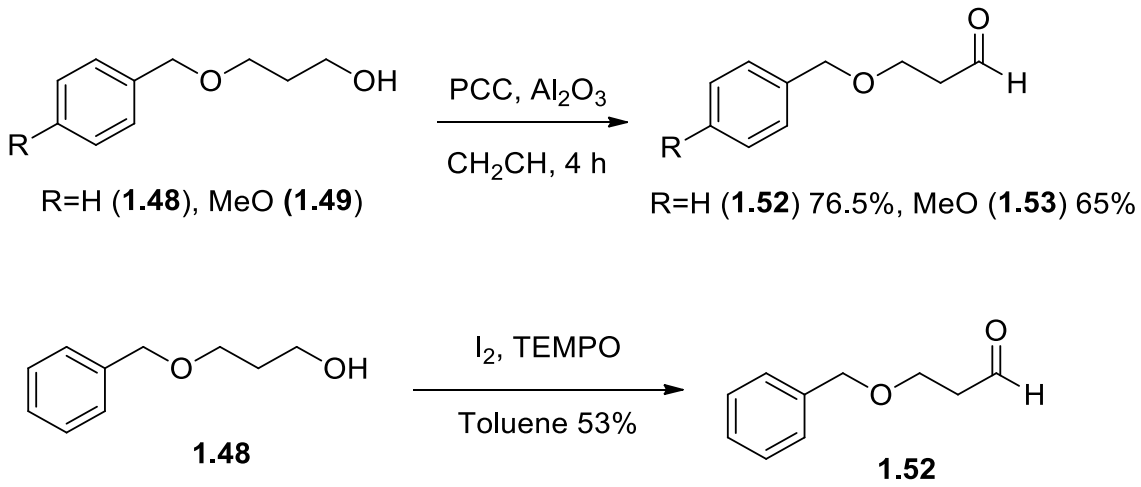
To pentadienylate aldehydes **1.52** and **1.53**, 5-bromopenta-1,3-diene (**1.59)** was synthesized according to Scheme 14. A Grignard reaction between vinyl magnesium bromide (**1.56)** and acrolein (**1.57)** produced alcohol **1.58.** Purification of **1.58** via distillation was difficult due to polymerization. Flash chromatography provided adequate purification, although product may be lost during solvent removal due to low boiling point, 55 ºC. Bromination of the alcohol gives (E)-5-bromopenta-1,3-diene (**1.59).**



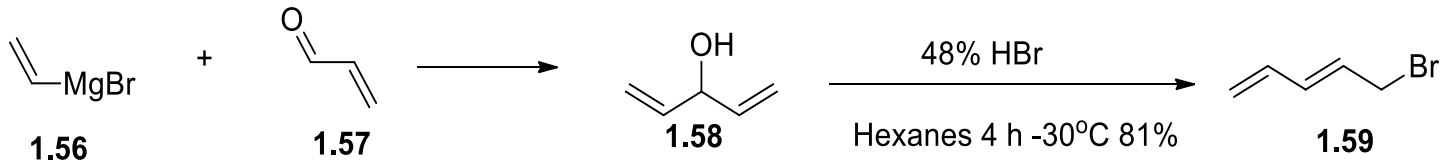
Scheme 11. Synthesis of Alcohols



Scheme 12. Attempted Reduction Using Chary-Laxmi method



Scheme 13. Synthesis of Aldehydes



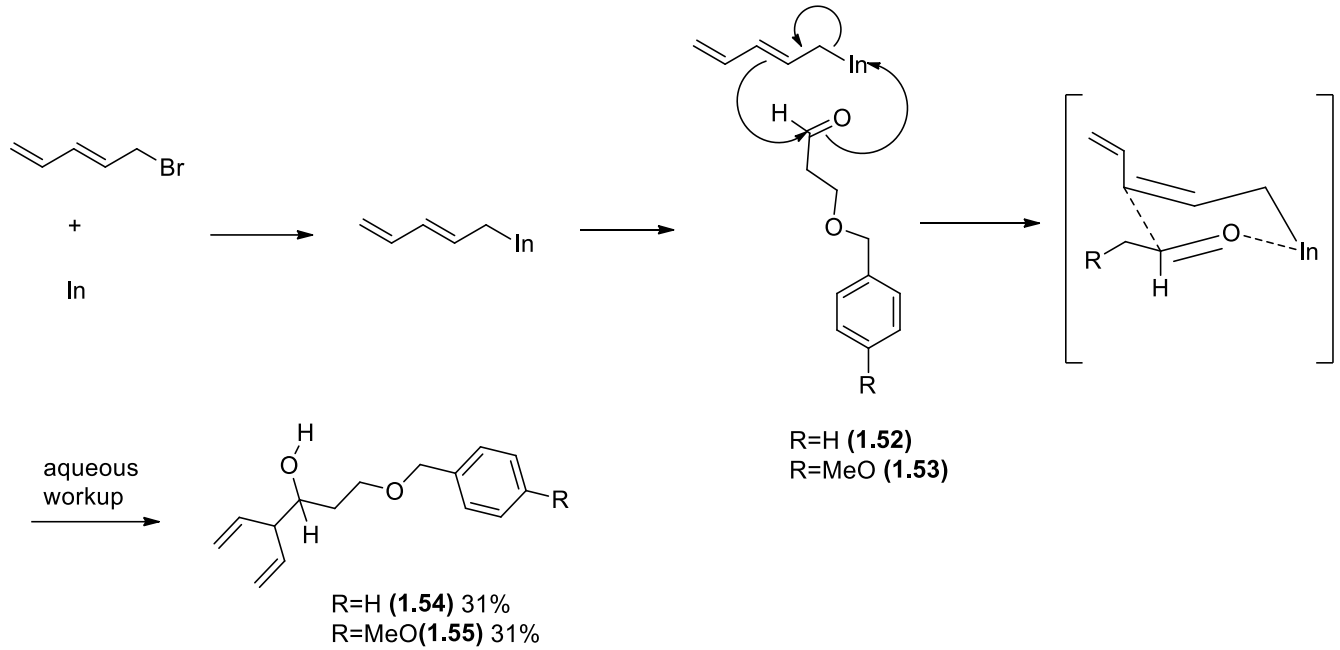
Scheme 14. Synthesis of (E)-5-bromopenta-1,3-diene

Aldehydes **1.52** and **1.53** were reacted with allylic bromide **1.59** in an indium-mediated coupling to produce **1.54** and **1.55**. Bromine was displaced with indium, and a six membered chair-like transition state was formed. The C-In bond was broken, and electrons are shifted to form a carbon-carbon bond. The indium was replaced with hydrogen during the aqueous workup (Scheme 15). Once the chemistry for the total synthesis of $PGF_{2\alpha}$ is elucidated, we will revisit controlling the stereochemistry of the hydroxyl group. For stereochemical control the chiral auxiliary (4R, 5R)-2-((1E, 3E)-penta-1, 3-dien-1-yl)-4, 5-diphenyl-1, 3-*bis* (phenylsulfonyl)-1, 3, 2-diazaborolidine (Image 3) will be used.[18] Before gaining total stereocontrol of the hydroxyl group, we will use iodocyclization to provide partial stereocontrol *via* enantiomers which will be used in the continuation of the $PGF_{2\alpha}$ synthesis.

1.6 Syntheses of 4-(iodomethyl)-6-methyl-1,3-dioxan-2-one model system for 4-(2-(benzyloxy)ethyl)-6-(iodomethyl)-5-vinyl-1,3-dioxan-2-one

Before the iodocyclization of **1.54,** a model synthesis of for 4-(iodomethyl)-6-methyl-1,3-dioxan-2-one was developed. The first step in synthesizing 4-(iodomethyl)-6-methyl-1,3-dioxan-2-one was the formation of pent-4-en-2-yl carbamate. Trichloroacetyl isocyanate and potassium carbonate were reacted with 4-penten-2-ol giving carbamate **1.60** for a 98% yield (Scheme 16). The product crystallized easily in ethyl acetate.[19]

Carbamate **1.61** was reacted with iodine in a biphasic solution of ether and saturated aqueous $NaHCO_3$. Initially a basic workup was used following the procedure from Holmes and Bartlett 1989.[20] Cyclization attempts using these conditions were unsuccessful (Scheme 17).



Scheme 15. Synthesis and Mechanism of 1-(benzyloxy)-4-vinylhex-5-en-3-ol and 1-((4-methoxybenzyl) oxy)-4-vinylhex-5-en-3-ol

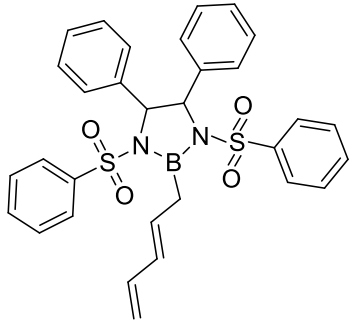
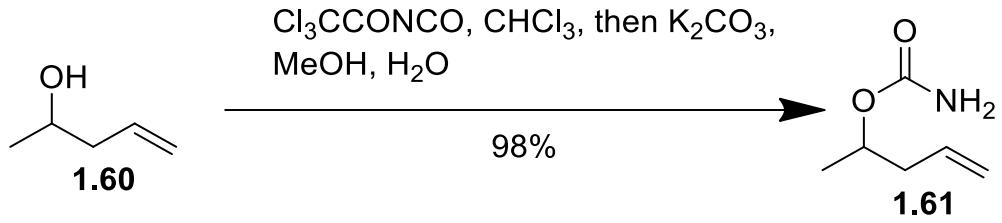
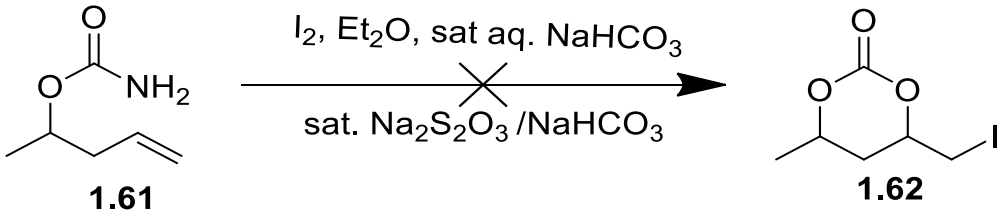


Image 3. Chiral Auxiliary (4R, 5R)-2-((1E, 3E)-penta-1, 3-dien-1-yl)-4, 5-diphenyl-1, 3-bis (phenylsulfonyl)-1, 3, 2-diazaborolidine



Scheme 16. Synthesis of Pent-4-en-2-yl Carbamate

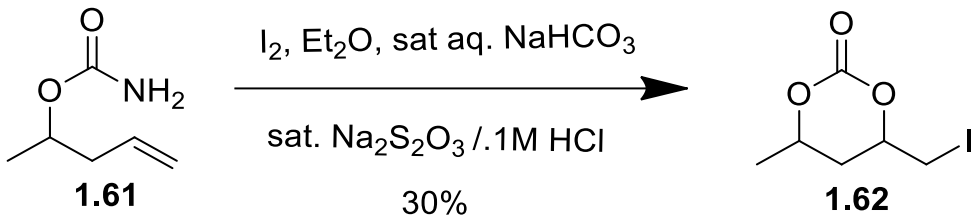


Scheme 17. Attempted Synthesis of 4-(iodomethyl)-6-methyl-1,3-dioxan-2-one Using Basic Work Up

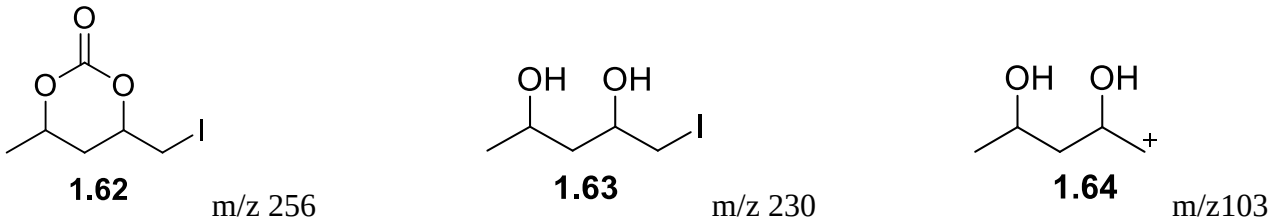
Guindon *et al.*[21] successfully performed the iodocyclization using $NaHCO_3$, silver triflate, and iodine in an acidic workup of silica gel and water. Scheme 18 shows where the basic workup in our synthesis was substituted for an acidic workup using 0.1 M HCl. The change in workup gave a successful reaction with a yield of 30% after flash chromatography.[22]

Initially, isolation of product was difficult. The reaction produced a UV active compound which gave a spot with an R_f value consistent with that expected for the cyclization product during TLC analysis. After isolation, it was discovered that the iodocyclization product, 4-(iodomethyl)-6-methyl-1,3-dioxan-2-one **(1.62)**, was extremely sensitive and decomposed in the presence of light and heat. The sensitivity resulted in difficulties during product concentration. Decomposition occurred at temperatures greater than 35 ^oC. To avoid extended concentration times, product solution temperature was reduced to 0 ^oC before being placed on rotovap while shielded from light. Presence of product is confirmed using GC/MS, (Figure 1).

To avoid further decomposition, the NMR sample was prepped immediately before analysis on the NMR. Samples were very difficult to analyze due to quick degradation. Figure 1 shows a GC chromatograph taken before and after NMR analysis. Ions 256, 230, and 103 were extracted to confirm presence of product and fragmentation products, (Scheme 19). Fragments 230 and 103 are produced after loss of CO_2 and CO_2 plus $I^{\cdot}$ Deuterated benzene gave better NMR results; however, benzene is not a preferred solvent due to high boiling point and potential loss of sample.



Scheme 18. Synthesis of 4-(iodomethyl)-6-methyl-1,3-dioxan-2-one Using Acidic Workup



Scheme 19. Reaction Product Fragmented and Products

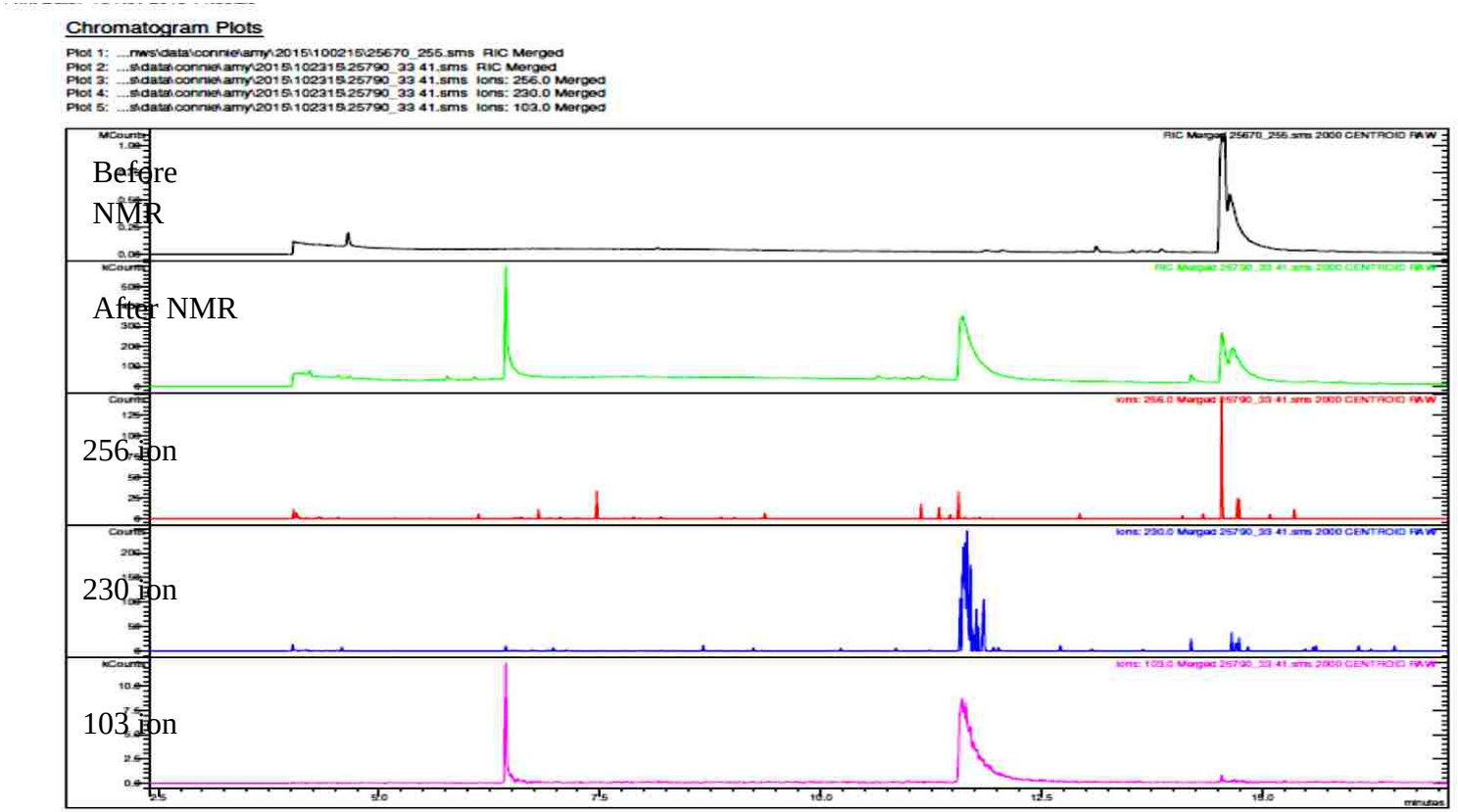
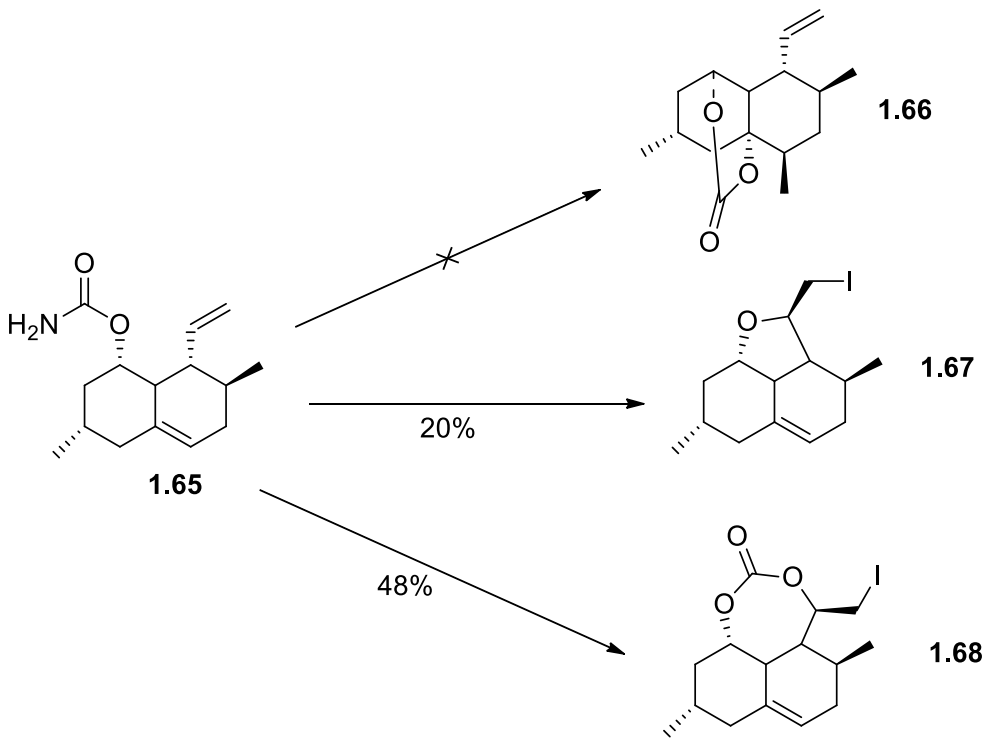


Figure 1. Chromatograph of Iodocyclization Product, Fragmented Product, and Extracted Ions 256, 230, and 103

A literature search of the proposed transformation produced limited results. The yields Hirama and Uei[23] reported for the iodocyclization product ranged from 54-96% on monosubstituted internal and terminal alkenes; however, reported yields reflected a mixture of cyclized and uncyclized product from reactions conducted on monosubstituted alkenes. The yields of only cyclized product ranged from 54% to 79% (Table 1).

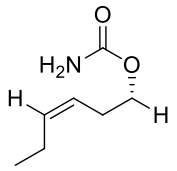
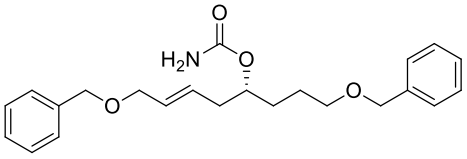
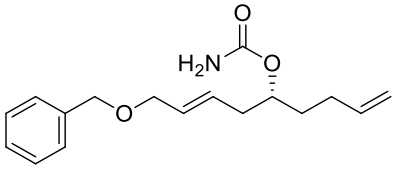
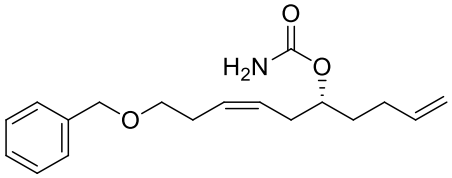
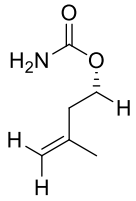
Hecker and Heathcock[24] attempted the transformation on a bicyclic compound with both terminal unsubstituted and internal alkenes. Reaction with the terminal alkene would give a seven-membered ring product and reaction with the internal alkene would give the six-membered ring product (Scheme 20). None of the six-membered ring product was isolated. A 48% yield of the seven membered ring product was isolated along with 20% yield of the tetrahydrofuran product. Due to difficulties with carbamate iodocyclization product stability, attempts to cyclize carbamate were discontinued. An alternative to the carbamate iodocyclization is the iodocyclization of carbonate **1.68** (Scheme 21). All initial attempts to synthesize *tert*-butyl pent-4-en-2-yl carbonate (**1.68**) produced a by-product, **1.69**, which accounted for approximately 50% of the crude yield. Yield is based on GC integration comparison (Figure 2) and (Table 2).

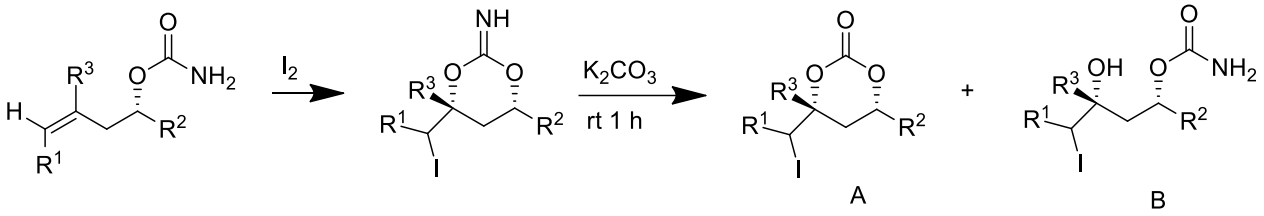
The $(Boc)_2O$ reagent used to make *tert*-butyl pent-4-en-2-yl carbonate contained contaminant, **1.70.** The similar polarities caused difficulties during purification. The by-products produced using Boc anhydride were possibly due to small size of the alcohol used in the model reaction (Scheme 22). Reference search showed that Boc anhydride was used to form carbonates using larger alcohols as starting material. After flash chromatography, the presence of all compounds was verified by GCMS. Purification of reaction crude was conducted on $AgNO_3$ 10% wt on silica gel. The volatility of **1.68** causes product loss during solvent removal.

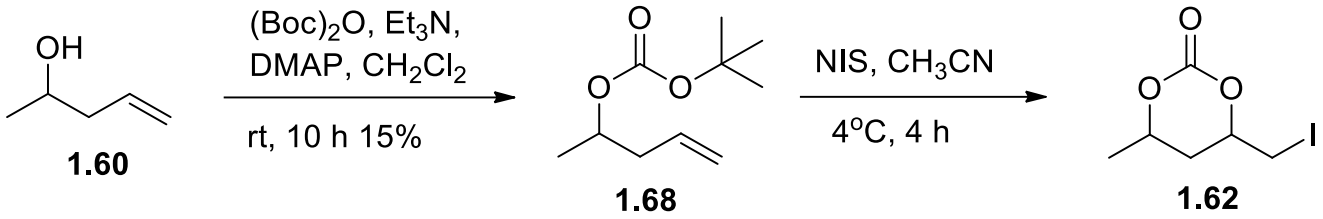


Scheme 20. Hecker and Heathcock Iodocyclization results

Table 1. Results from Hirama and Uei Iodocyclization Reactions

Substrate	Rxn, T (hr)	A:B	A+B (%)	A (%)	Stereoselectivity
	3	100:0	68	68	
	39	4.4:1	76	62	14:1
	41	4.1:1	71	56	14:1
	42	4.6:1	96	79	10:1
	26	~100:0	54	54	





Scheme 21. Synthesis of 4-(iodomethyl)-6-methyl-1,3-dioxan-2-one *via* Carbonate Cyclization

Table 2. Integration of *tert*-butyl pent-4-en-2-yl Carbonate Reaction Mixture

Compound	Integration	% Yield
1.68	1.52e+8	49%
1.69	1.42e+8	46%
1.70	1.42e+7	5%

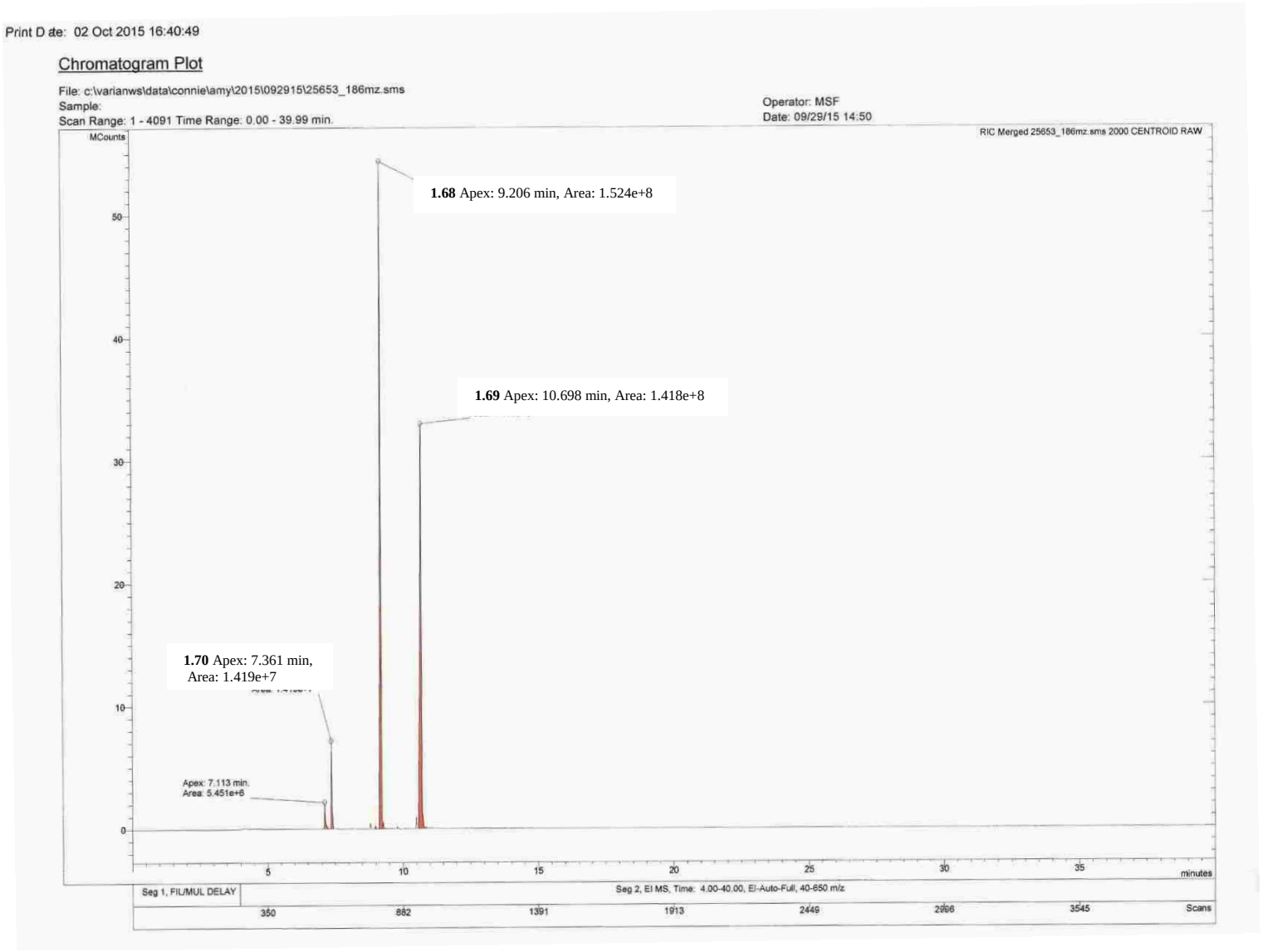
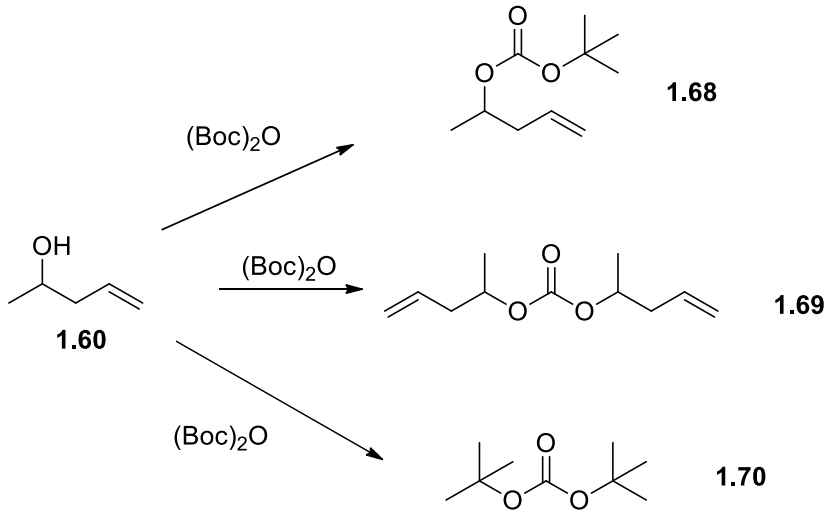


Figure 2. GC of *tert*-butyl pent-4-en-2-yl carbonate Reaction Mixture.

To avoid by-products produced in the previous reaction, pent-4-en-2-ol was reacted with Boc-ON (2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile) and *n*-BuLi at 0°C for 4 h[27] for an 89% crude yield (Scheme 23).

The reaction gave nearly exclusive product as shown in GC/MS and NMR spectra (Figure 3). Reacting pent-en-2-ol with Boc-ON was a successful alternative in producing t*ert*-butyl pent-4-en-2-yl carbonate without by-products. Boc anhydride was used in the target reaction system. By-products produced in the model reaction were not expected with the target alcohol due to larger size. *Tert*-butyl pent-4-en-2-yl carbonate was reacted with NIS (*N*-iodosuccinimide) in CH_3CN at 4°C for nine hours.[25] Previous synthesis of 4-(iodomethyl)-6-methyl-1,3-dioxan-2-one by Duan gave product in major to minor isomer ratios of 10:1; 14:1; 21.1:1 using the following conditions respectively: I_2/CH_3CN -20°C; IBr/CH_2Cl_2 -80°C; IBr/PhMe -80°C.[27] The chemical shift, integrations and GC integrations confirming the results are shown on Table 2, Table 3, and Figure 2.

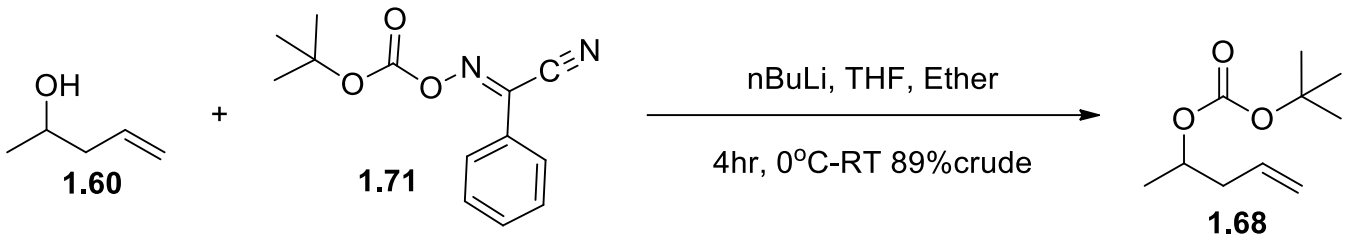
Major and minor isomers were confirmed when comparing peak chemical shifts and splitting patterns to NMR data reported by Duan (Table 4). Problems with compound decomposition observed earlier in carbamate iodocyclization appeared to be avoided with the carbonate cyclization method; however, a large portion of the crude product crystalizes during transfer onto the chromatography column. Upon solvent removal the product is a clear yellow oil and did not readily change color when prepped for NMR analysis.



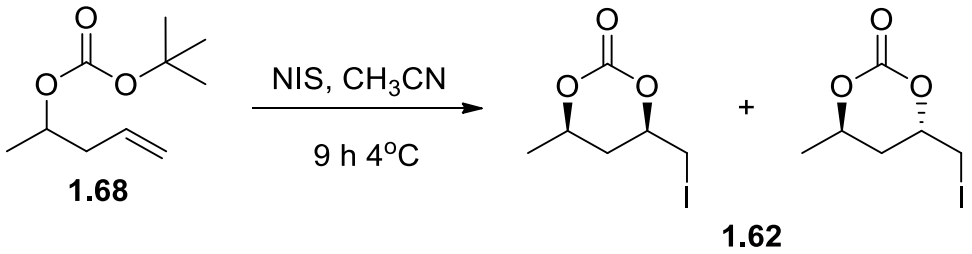
Scheme 22. *Tert*-butyl pent-4-en-2-yl carbonate and By-Products from pen-4-en-2-ol Reaction with Boc Anhydride.

Table 3 Reaction Conditions for Synthesis of tert-butyl pent-4-en-2-yl carbonate

Reaction #	OH (molar eq)	$(Boc)_2O$ (molar eq)	DMAP (molar eq)	Base (reagent, molar eq)	Solvent	Reaction Time
1	1	1.5	.5	Imidazole, 4	CH_3CN	5 h
2	1	2	.5	Et_3N, 2	CH_2Cl_2	12 h
3	1	1.5	.02	Et_3N, .4	CH_2Cl_2	10 h
4	1	1	.5	0	CH_3CN	7 h



Scheme 23. Synthesis of Carbonate 1.68 using Boc-ON and n-BuLi.



Scheme 24. Synthesis of 4-(iodomethyl)-6-methyl-1,3-dioxan-2-one from Carbonate

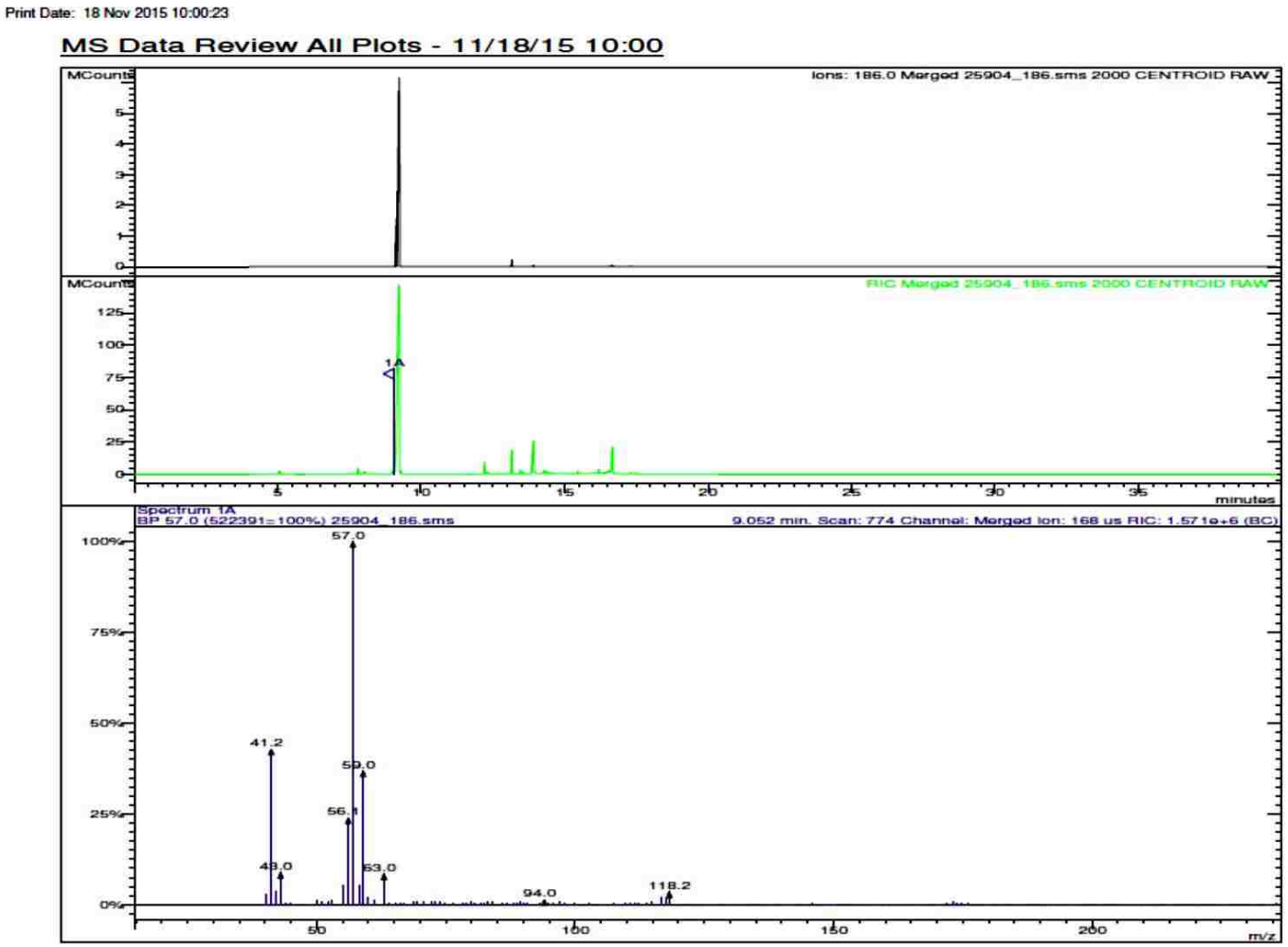


Figure 3. GC/MS Chromatograph and Spectra of *tert*-butyl pent-4-en-2-yl Carbonate Reaction Crude Using Duan, J. J. W.; Smith, A. B. procedure[27], EI (filament voltage 70 eV)

Table 4. Integration and Chemical Shifts of Major and Minor Iodocyclization Product from 4-(iodomethyl)-6-methyl-1,3-dioxan-2-one Crude, Spectra of Major and Minor Isomers Product

Major Split Pattern	d, 3	td, 1	td, 1	dd, 1	dd, 1	m, 1	m, 1
Chemical Shift (ppm)	1.45	1.7	2.4	3.26	3.31	4.47	4.63
Integration	3	1.59	1.25	1.15	1.08	1.2	1.37
Minor Split Pattern	d, 3	m, 1	m, 1	dd, 1	dd, 1	m, 1	m, 1
Chemical Shift (ppm)	1.49	2.14	2.25	3.31	3.48	4.63	4.72
Integration	1.83	1.04		0.23	0.33	1.37	0.54

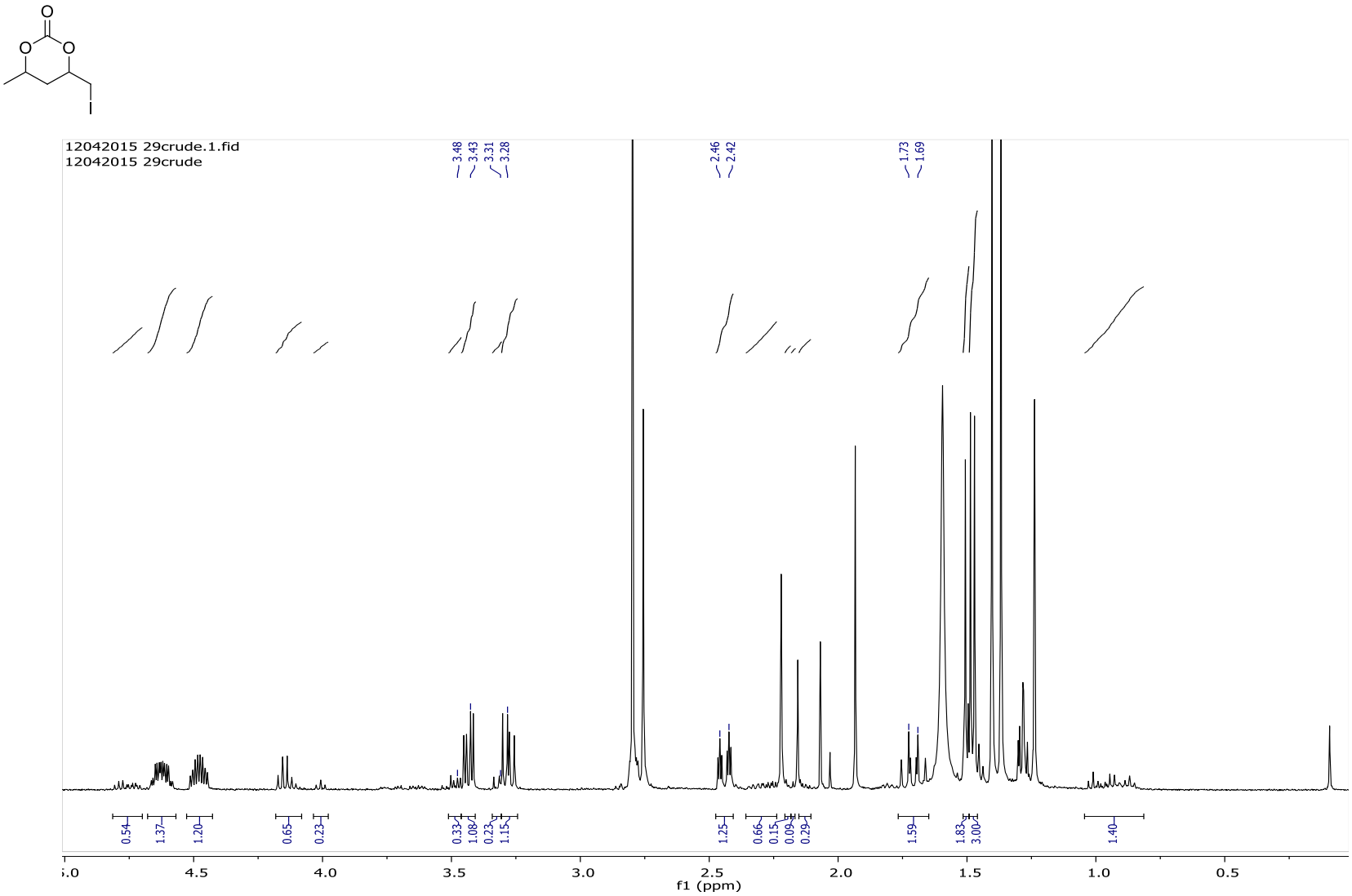


Figure 4. 4-(iodomethyl)-6-methyl-1,3-dioxan-2-one Crude, Spectra of Major and Minor Isomers Product from Mohapatra, D.K.; Bhimreddy, E. Procedure[25]. (^{1}H-NMR 400MHz)

Table 5. Reference Splitting Patterns and Chemical Shifts of Reaction Product (H^1 500MHz)[7]

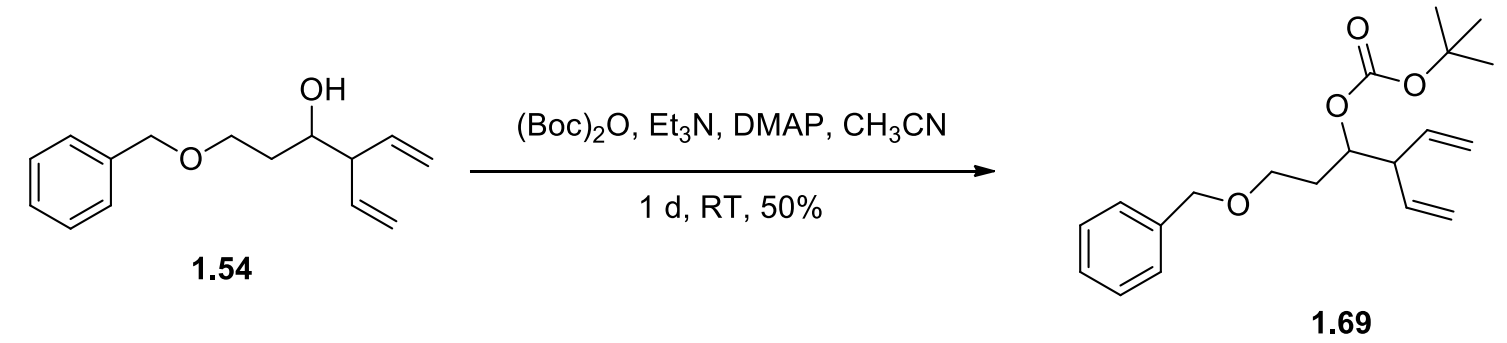
	d, 3	td, m, 1	td, m, 1	dd, 1	dd, 1	m, 1	m, 1
Major	1.45	1.69	2.41	3.27	3.41	4.43-4.48	4.57-4.64
Minor	1.48	2.09-2.14	2.22-2.28	3.3	3.46	4.60-4.65	4.68-4.74

1.7 Synthesis of 4-(2-(benzyloxy)ethyl)-6-(iodomethyl)-5-vinyl-1,3-dioxan-2-one

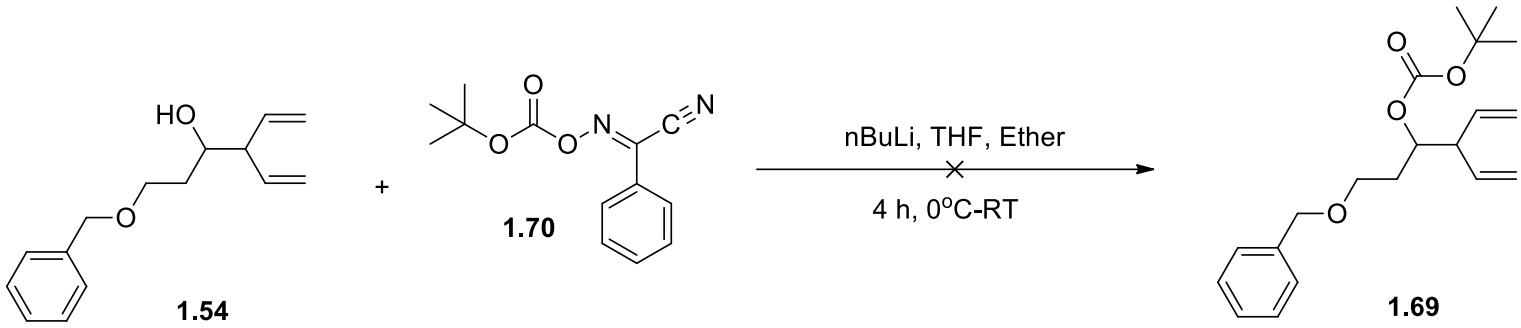
Carbonate **1.69** was formed at a 50% yield by coupling alcohol **1.54** with Boc anhydride *via* Steglich esterification (Scheme 25).[26] During solvent removal a red insoluble solid formed. Low product yield is possibly due to product entrapment in solid. Initial review of crude ^{1}H NMR shows chemicals integrations similar to the expected product (**1.69)** (Figure 5). However, after purification, ^{1}H NMR data revealed only starting materials (Figure 6).

A diastereoselective I_2 induced electrophilic cyclization was performed when carbonate **1.69** was reacted with NIS at -50^{o}C, giving **1.71** for a 65% yield. Mohaptra *et al*. performed the iodocyclization in their synthesis of polyrhacitide A. They discovered that the iodo-carbonate was unstable during extended storage and purification must be performed quickly using flash chromatography.[25] Table 7 shows the results of previously reported iodocyclization reaction results

The procedures from Mohaptra and Rajesh used NIS in acetonitrile at -20^{o}C gave a single product. However, the conditions reported by Duan result in mixtures of stereoisomers, (Scheme 28 and Table 6).[27]



Scheme 25. Synthesis of Carbonate **1.69** Using Steglich Esterification



Scheme 26. Attempted Synthesis of Carbonate **1.69** Using BOC-ON.

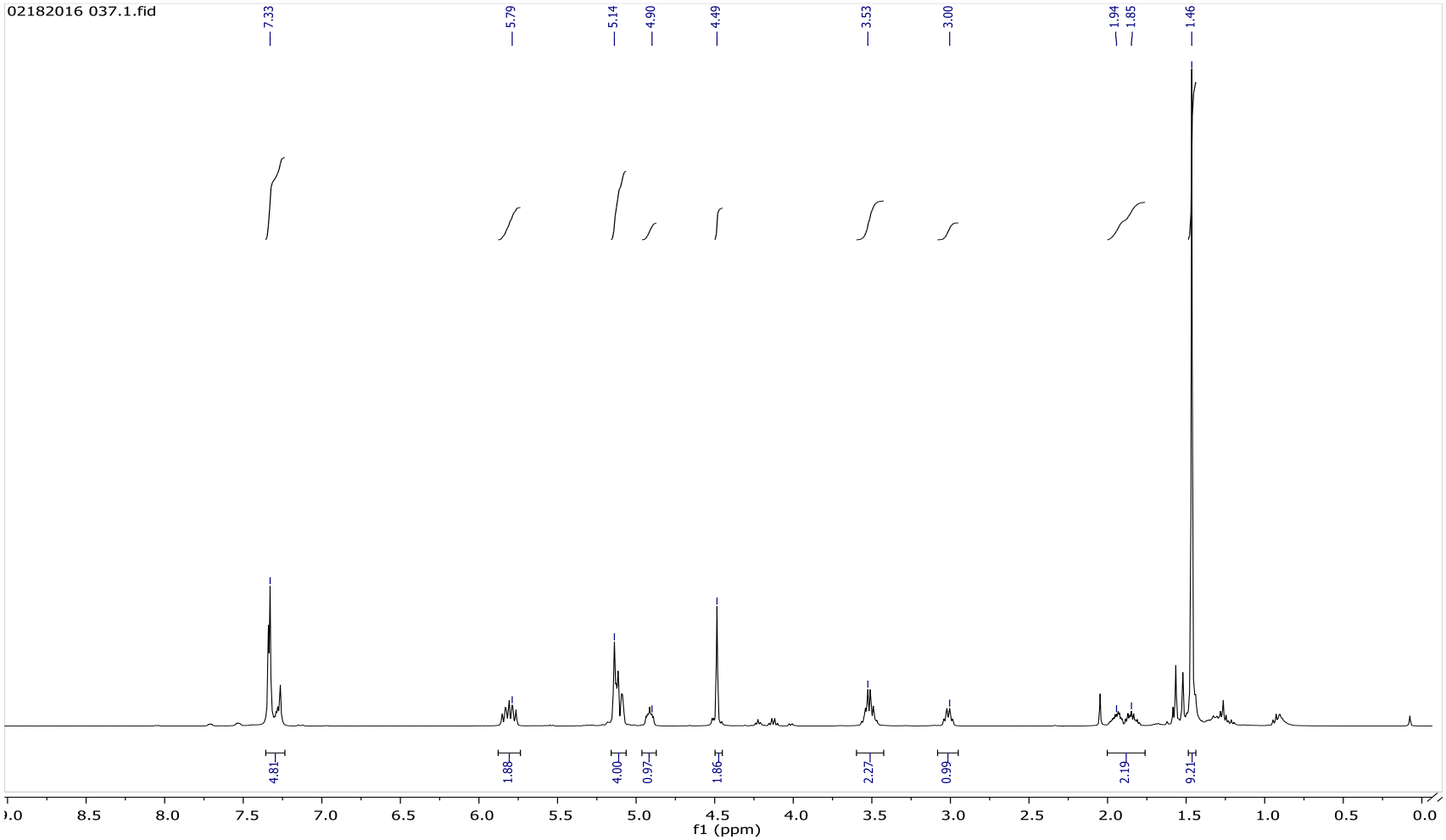


Figure 5. ^{1}H NMR of 1-(benzyloxy)-4-vinylhex-5-en-3-yl tert-butyl carbonate, **1.69**

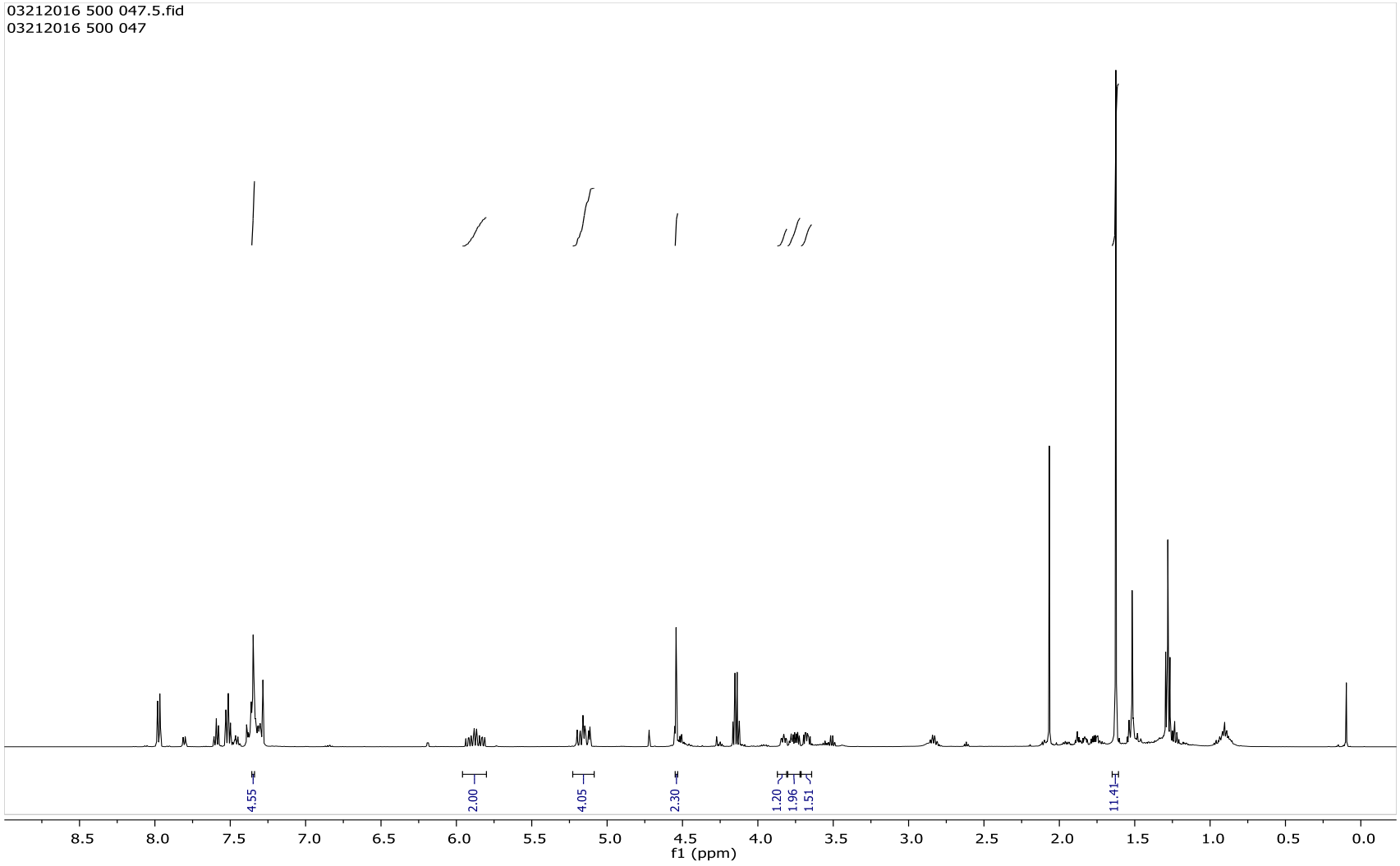


Figure 6. ^{1}H NMR of BOC-ON Unsuccessful Reaction Crude with Chemical Shifts Similar to Chemical Shifts of Reaction Product

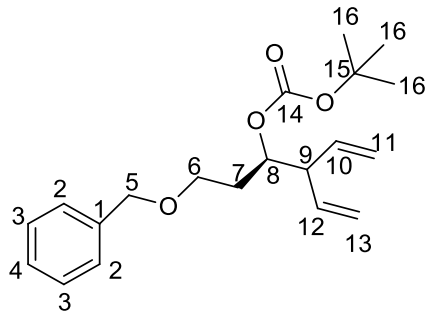
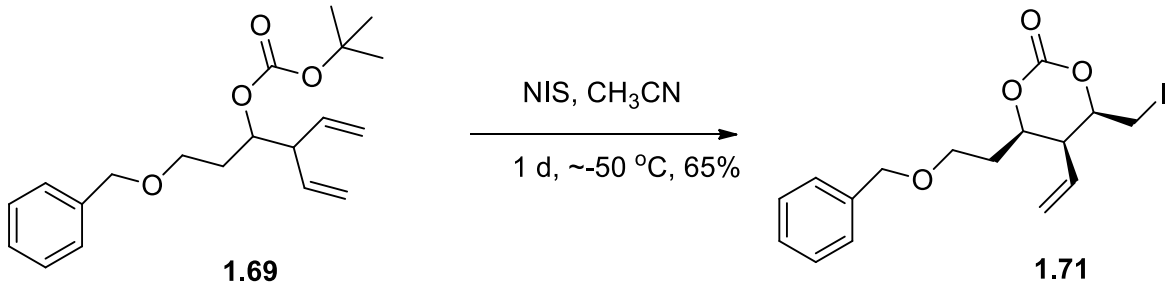


Table 6. Chemical shifts of 1-(benzyloxy)-4-vinylhex-5-en-3-yl *tert*-butyl carbonate Protons

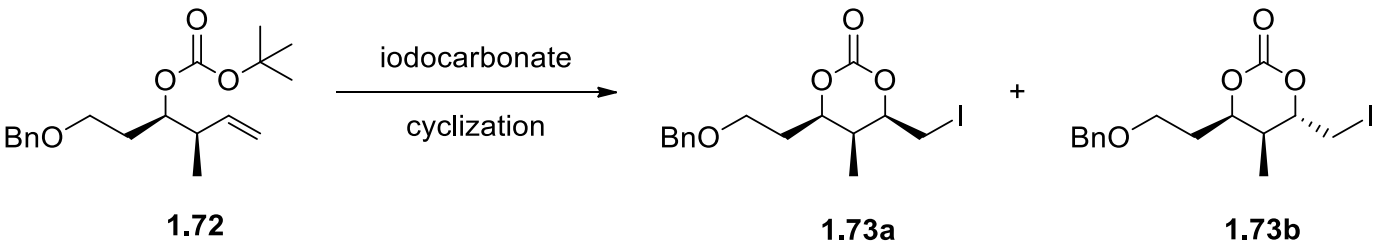
Proton	H2-4	H5	H6	H7	H7'	H8	H9	H10,12	H11, 13	H16
Chemical Shift, ppm	7.21	4.49	3.53	1.85	1.94	4.9	3	5.79	5.14	1.46



Scheme 27. Iodocyclization of 1-(benzyloxy)-4-vinylhex-5-en-3-yl *tert*-butyl carbonate

Table 7. Results and Conditions

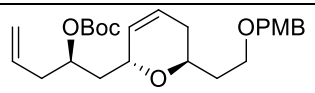
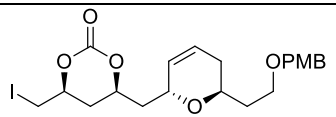
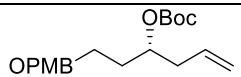
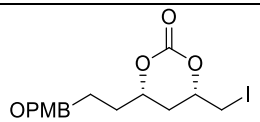
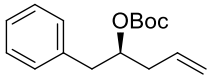
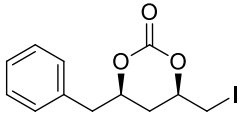
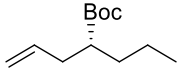
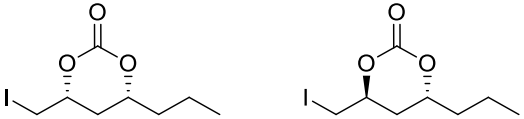
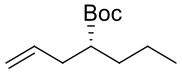
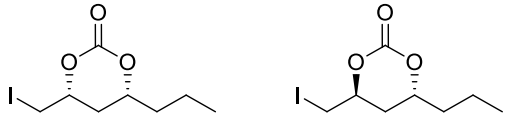
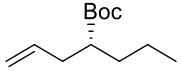
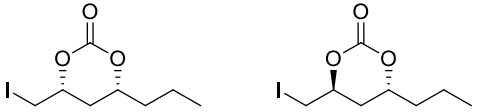
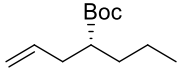
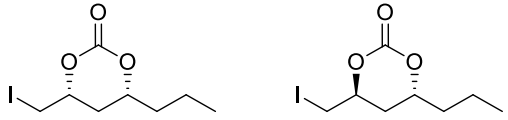
	I, reagent	Solvent	Temp.	Time	Yield	Ratio a:b
1	I_2	CH_3CN	-20°C	6.5 hr	79	5.7:1
2	IBr	CH_3CN	-20°C	15 min	67	3.1:1
3	IBr	CH_2Cl_2	-20°C	15 min	75	3.3:1
4	IBr	CH_2Cl_2	-85°C	15 min	74	7.7:1
5	IBr	CH_2Cl_2	-94°C	15 min	83	8.7:1
6	IBr	Et_2O	-110°C	15 min	75	7.3:1
7	IBr	PhMe	-80 to -85°C	11hr	85	13.9:1



1.72 **1.73a** **1.73b**

Scheme 28. IBr Induced Cyclization by Duan and Smith

Table 8. Comparison of Previously Reported Iodocyclization Reaction Results

Group/Year	Starting Material	Conditions	Products	Stereochemical Ratios	Yield
Mohapatra/ 2010		NIS, CH_3CN, 0 ^oC 1hr		100%	92%
Rajesh/ 2009		NIS, CH_3CN, -20 ^oC 12hr		100%	85%
Kumar/ 2011		NIS, CH_3CN, -40-0 ^oC 1.5hr		100%	89%
Duan/ 1993		I_2, CH_3CN, -80 to -85 ^oC 30min		7.7:1	73%
Duan/ 1993		IBr, THF, -80 to -85 ^oC 30min		10.0:1	89
Duan/ 1993		IBr, toluene, -20 ^oC 30min		8.4:1	90
Duan/ 1993		ICl, CH_2Cl_2 -80 to -85 ^oC 30min		5.8:1	85

1.8 Discussion of Stereochemical Assignments

Figure 7 shows the ^{1}H NMR of both major and minor diastereomers of **1.71**. The chemical shifts, splitting patterns, and coupling constants (J) of the spectra are presented in Table 9. The first step in confirming the stereochemistry was verifying the backbone protons. The connectivity of carbons 6, 7, 8, 9, 10, 11, and 12 was confirmed by COSY NMR (Figure 8). Starting at cross peak (1.85, 3.68) corresponding to the proton pair 6 and 7, backbone connectivity can be traced to cross peak (1.85, 4.80) corresponding to the proton pair 7 and 8; to cross peak (2.97, 4.80) corresponding to the proton pair 9 and 8; to cross peaks (2.97, 4.69) and (2.96, 5.57) corresponding to the proton pairs 9 and 10, and 9 and 12 respectively.

Tracing from cross peak (2.97, 4.69) to cross peak (3.02, 4.71) corresponding to the proton pair 11 and 10, completes the backbone chain. The carbons and their corresponding protons are confirmed by HSQCDEPT (Figure 9).[28] CH_2s are denoted by the blue cross peaks. Table 11 lists each carbon chemical shift and the carbons and protons. In additional to the COSY, the ROESY confirms through space interactions of protons 8, 9, and 10; however, the exact stereochemistry was not confirmed by ROESY (Figure 10).

Expansions of the signals for protons 8, 9, 10 and 12 are shown in figures 11-16. The signals for H-10 (Figure 12) and H-8 (Figure 11) exhibit splitting patterns and coupling constants (J) that are consistent with the expected structure. In both cases a ddd is observed with three different coupling constants corresponding to the distinctly different conformational relationships of the three vicinal protons responsible for the splitting.

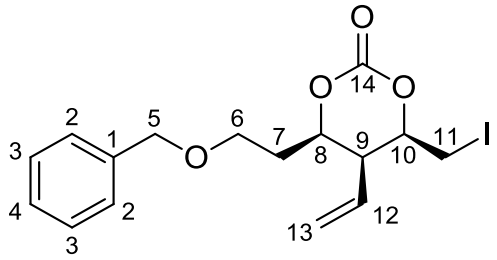


Table 9. Chemical Shift (δ), Splitting, and Coupling Constant (J, Hz) values for H-NMR of 1.71.

Proton	H2-4	H5-H5’	H6	H6'	H7	H7’
δ	7.34	4.51	3.68	3.58	1.95	1.84
splitting	m	ABq,	ddd	dt	dddd	dddd
J (Hz)		J_{AB}= 11.8 Hz, □□$_{AB}$ = 21.5 Hz	9.8, 9.3, 4.2	9.8, 5.0	12.3, 8.0, 5.0, 4.2	12.3, 9.3, 5.0, 4.3

Proton	H9	H8	H10	H11	H11’	H12, 13	H13'
δ	2.96	4.79	4.69	3.33	3.03	5.60 – 5.50	5.47 – 5.36
splitting	ddd	ddd	ddd	dd	t	m	m
J (Hz)	9.8, 2.8, 2.6	8.0, 4.7, 2.6	10.0, 4.9, 2.8	10.0, 4.9	10.0		

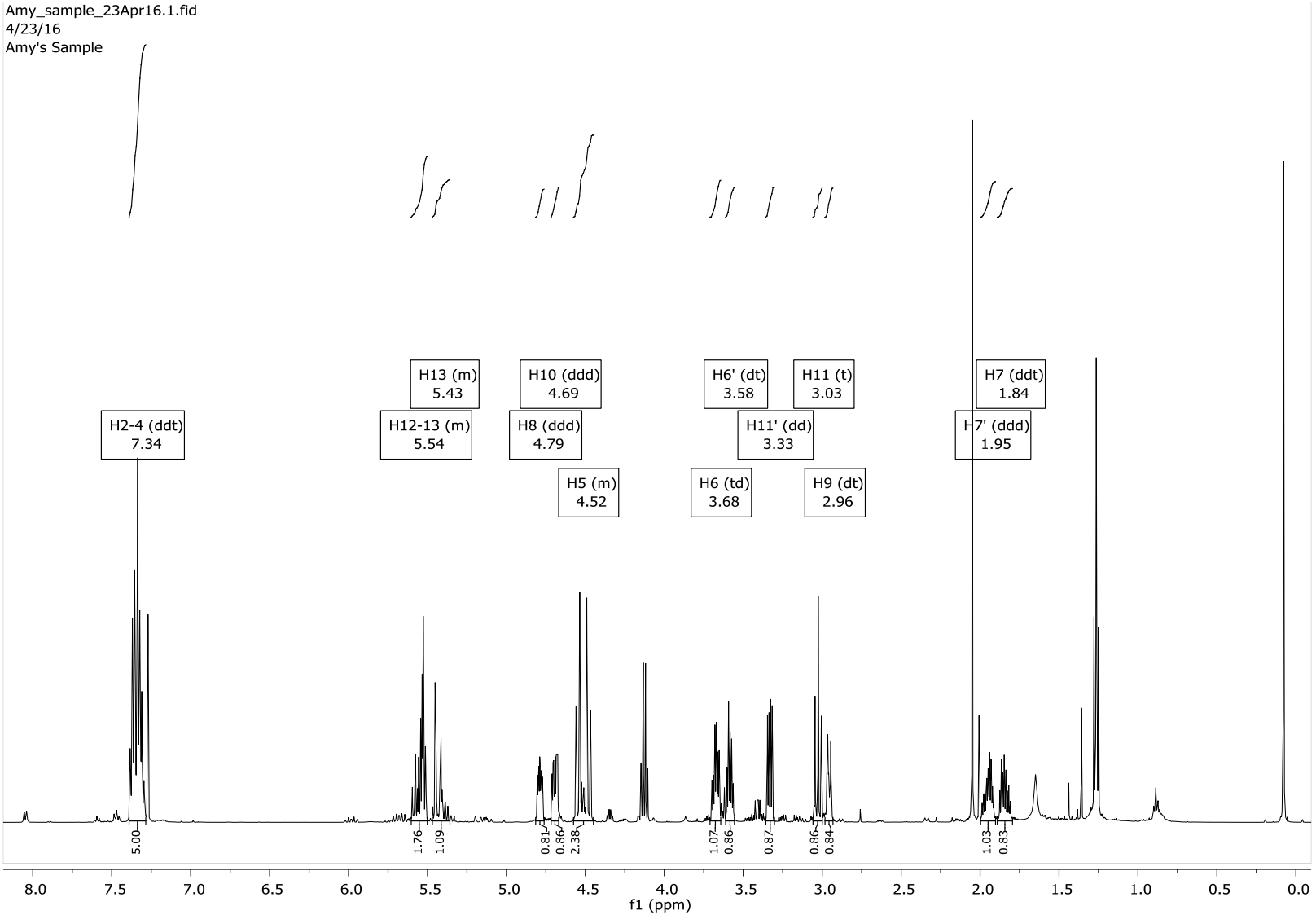


Figure 7. NMR of 4-(2-(benzyloxy)ethyl)-6-(iodomethyl)-5-vinyl-1,3-dioxan-2-one

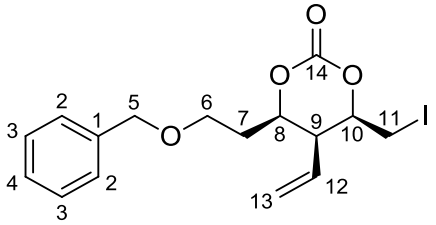


Table 10. Cosy Cross Peaks 4-(2-(benzyloxy)ethyl)-6-(iodomethyl)-5-vinyl-1,3-dioxan-2-one

Proton	6, 7	7, 8	9, 8	9, 10	9, 12	11, 10
Cross peak	3.68, 1.85	1.85, 4.80	2.97, 4.80	2.97, 4.69	2.96, 5.57	3.02, 4.71

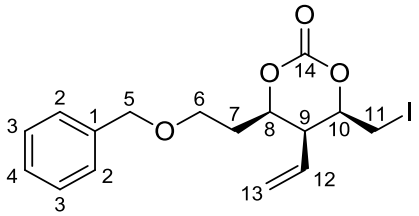


Table 11. HSQCDEPT Cross Peaks 4-(2-(benzyloxy)ethyl)-6-(iodomethyl)-5-vinyl-1,3-dioxan-2-one

	1-4	5	6	6’	7	7’	10	9	8	12	13	13’	11	‘11
C, ppm	127.7	73.2	65.0	65.0	33.4	33.0	80.5	42.28	78.8	125.6	124.6	124.4	1.4	1.7
H, ppm	7.33	4.49	3.60	3.60	1.86	1.86	4.69	2.97	4.80	5.59	5.45	5.54	3.02	3.02

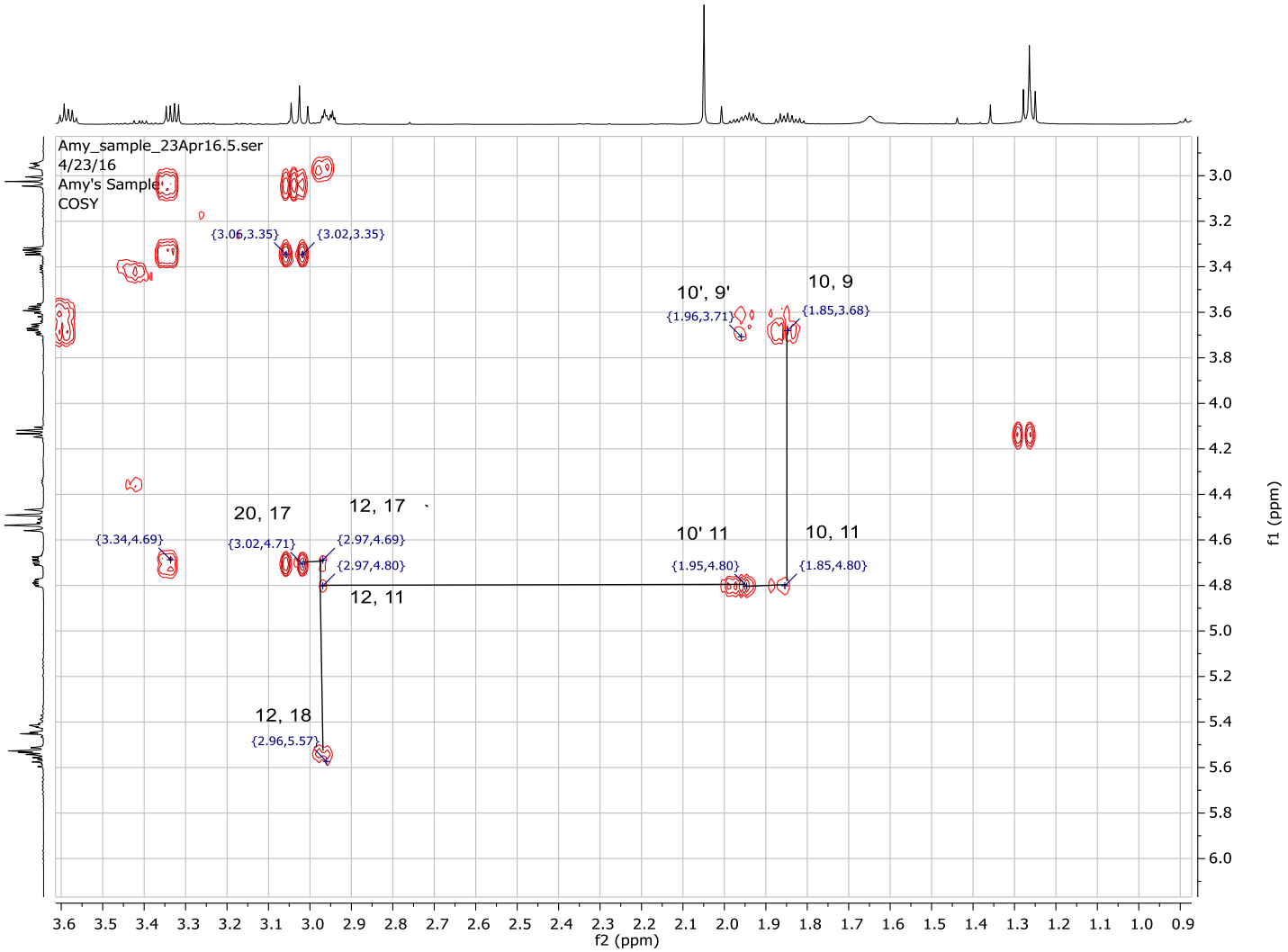


Figure 8. Cosy of 4-(2-(benzyloxy)ethyl)-6-(iodomethyl)-5-vinyl-1,3-dioxan-2-one

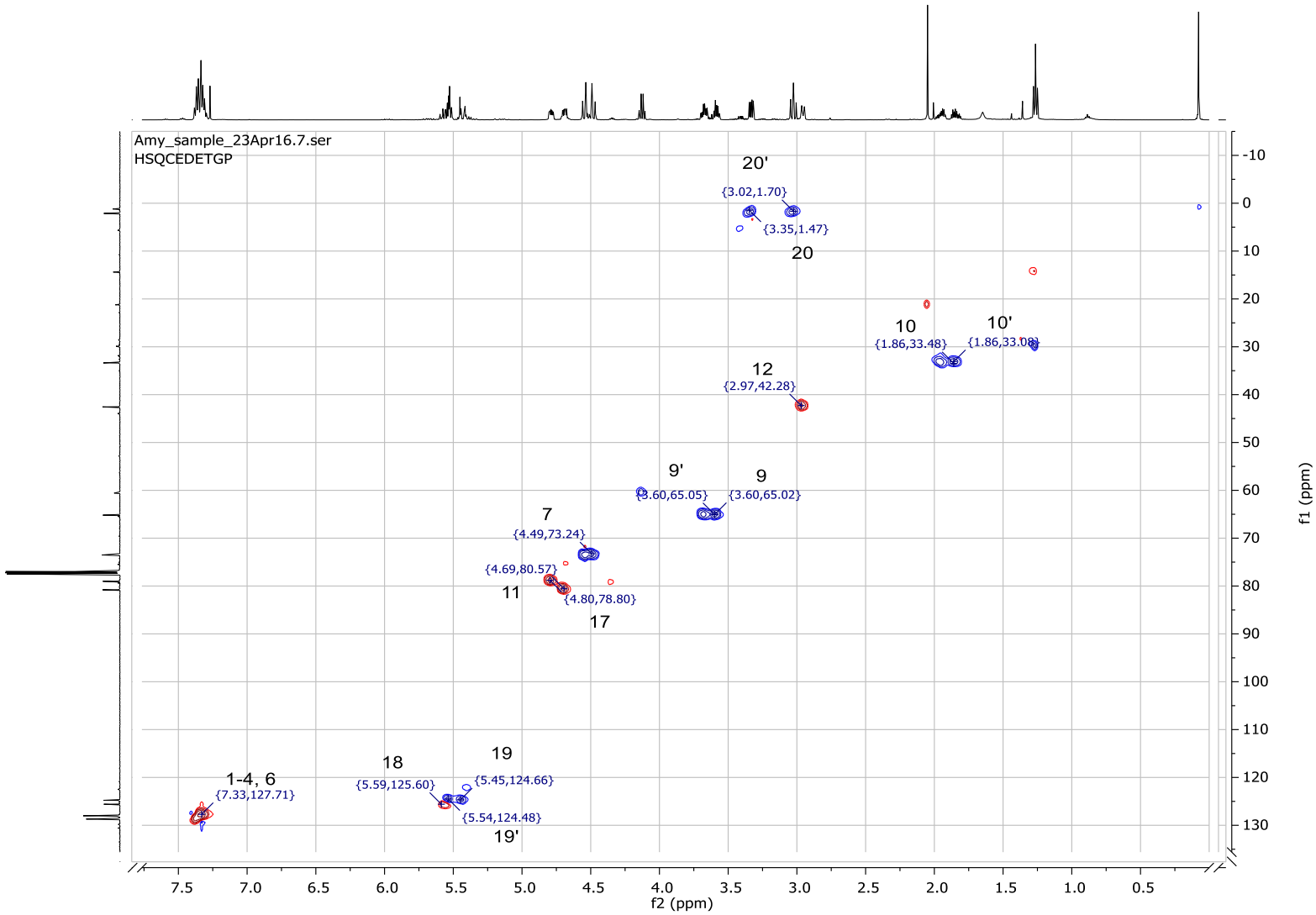
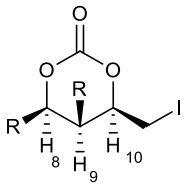


Figure 9. HSQCDEPT of 4-(2-(benzyloxy)ethyl)-6-(iodomethyl)-5-vinyl-1,3-dioxan-2-one



H	8	9	10
ppm	4.7	2.95	4.78

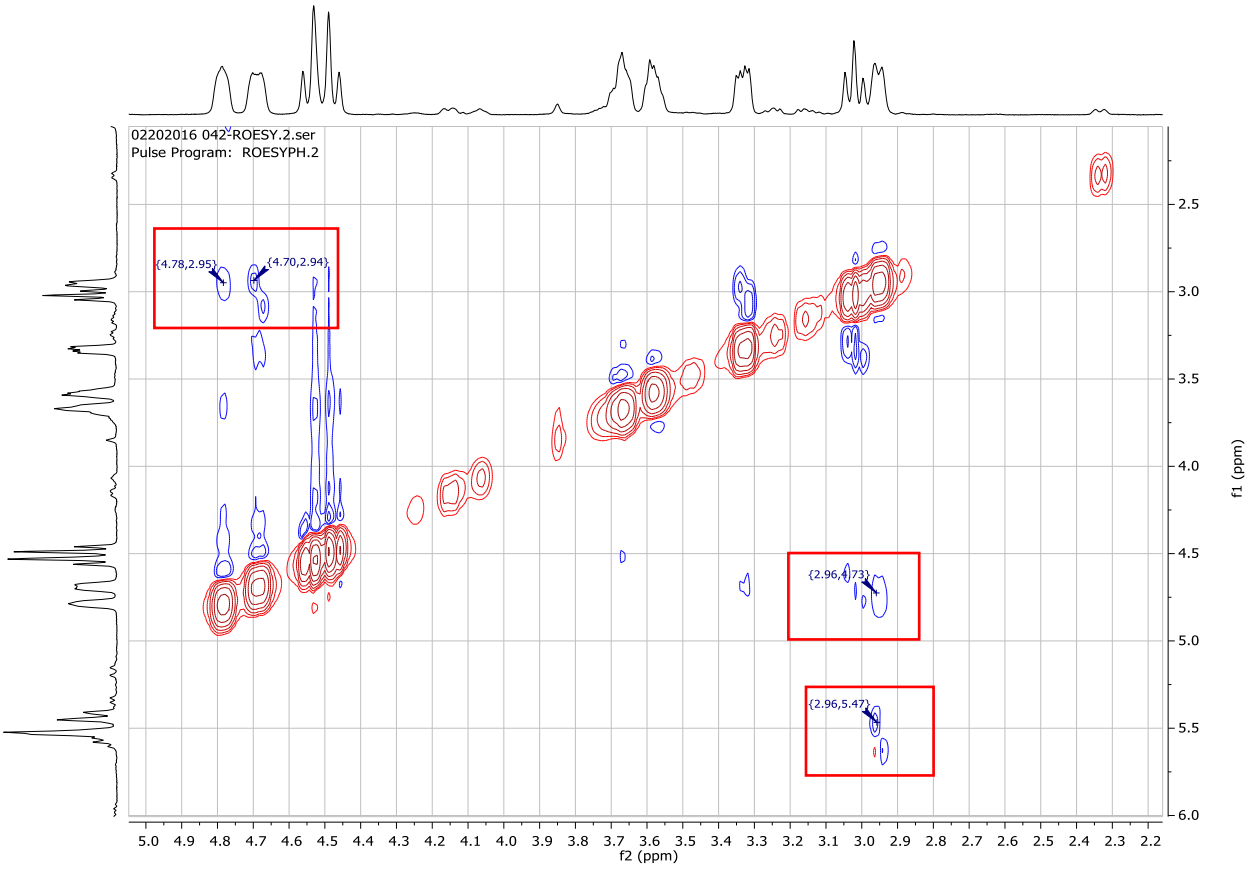


Figure 10. Roesy of 4-(2-(benzyloxy)ethyl)-6-(iodomethyl)-5-vinyl-1,3-dioxan-2-one

Figure 13 shows that the signal for the internal vinyl proton, H-12, is obscured by overlap with one on the signals for a terminal alkene proton (H-13)—a very unusual situation that: (a) may be explained by a magnetic anisotropic shielding interaction with the carbonate π system; or (b) may have some bearing on the assignment of stereochemistry at carbon 9.

H-12 is positioned directly above the pi electron density of carbonate. The deshielding effects of the delocalized pi system shifts the proton's peak upfield. The peak split pattern is undefined due to overlap with H-13 (Figure 13). This shielding effect strongly indicates that the vinyl group attached to C-9 occupies a pseudoaxial position on the carbonate ring. This, in turn, suggests that the pseudoaxial vinyl group is flanked by pseudoequatorial substituents on the adjacent C-8 and C-10 positions on the ring.

H-9 is split by both H-12 giving a doublet which is then split by the protons of H-8 and H-9 giving a doublet of triplet (Figure 15). Homonuclear decoupling of H-12 causes H-9 to collapse to a triplet with a coupling constant of 2.7 Hz. The small coupling constant indicates gauche relationships between H-9 and the neighboring protons on the carbonate ring, H-8 and H-10. Indeed, the small coupling constant establishes the stereochemistry of the molecule where the substituents on C-8, C-9, and C-10 are mutually cis.

Iodine's gauche position to oxygen may be due to stabilization achieved through alignment of electron-rich C–H and C–C bonds anti to the polar C–O and C–I bonds (accounting for the gauche effect by hyperconjugation). The position of the I is confirmed by the split patterns of H-11a and H-11b. The observed triplet for H-11b is due to splitting by similar geminal ($J_{11a,\ 11b}$) and vicinal ($J_{10,11b}$) coupling constants. The large vicinal coupling constant results from the anti relationship of H-11b and H-10.

H-8

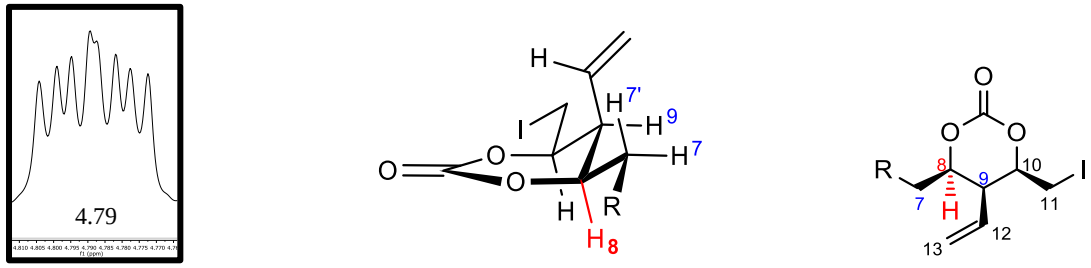


Figure 11. ^{1}H NMR (500 MHz, Chloroform-d) δ 4.79 (ddd, J = 8.0, 4.7, 2.6 Hz, 1H),

H-10

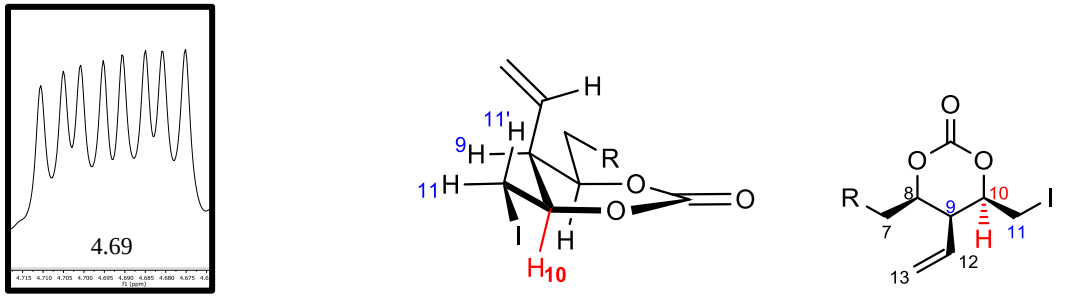


Figure 12. ^{1}H NMR (500 MHz, Chloroform-d) δ 4.69 (ddd, J = 10.0, 4.9, 2.8 Hz, 1H)

.

H-12 H-13 (overlapping signals)

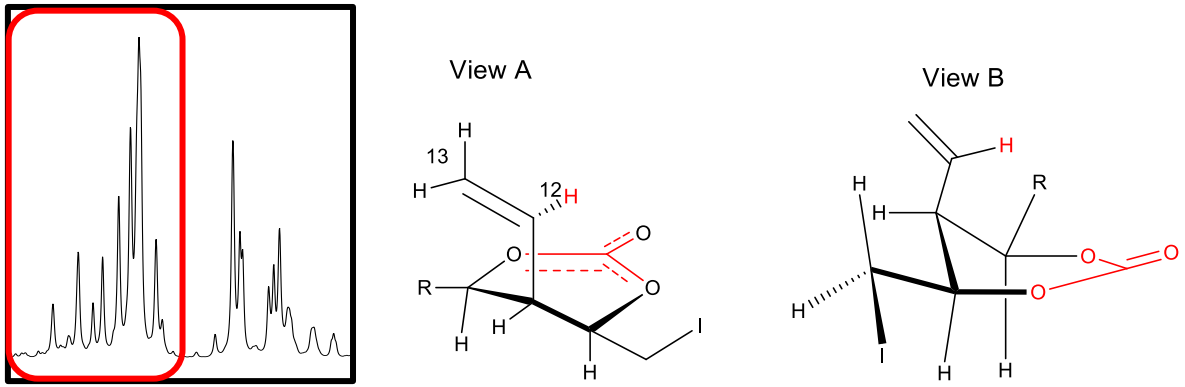


Figure 13. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.36: 5.48 – 5.43 (m, 1H).

H-9

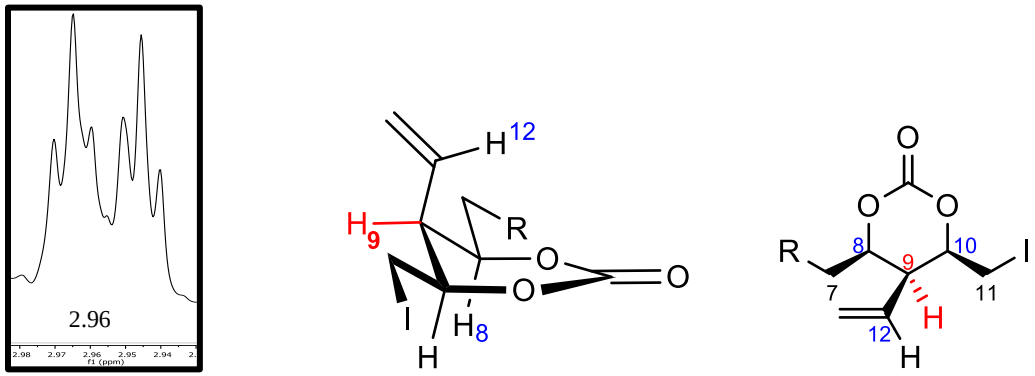


Figure 14. ^{1}H NMR (500 MHz, Chloroform-d) δ 2.96 (dt, J = 9.8, 2.7 Hz, 1H)

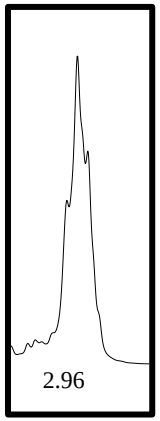
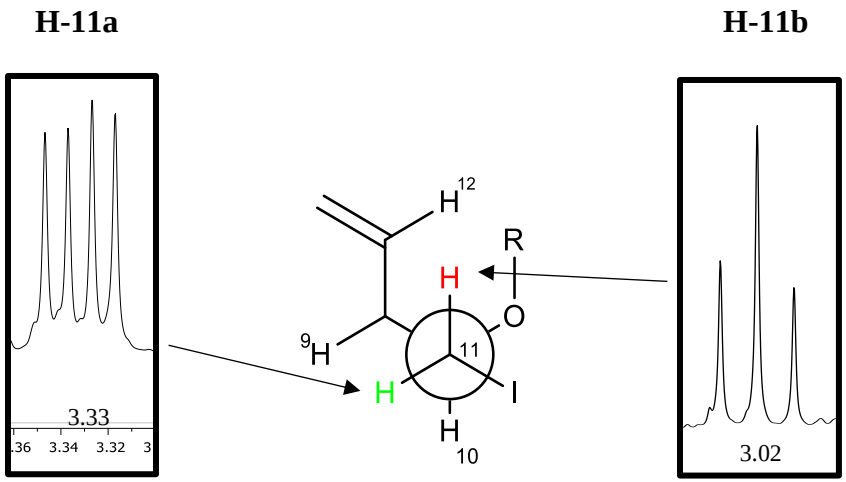


Figure 15. ^{1}H NMR Homonuclear Decoupling (500 MHz, Chloroform-d) δ 2.96 (t, J = 2.7 Hz, 1H),



^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.33 (dd, *J* = 10.0, 4.9 Hz, 1H),

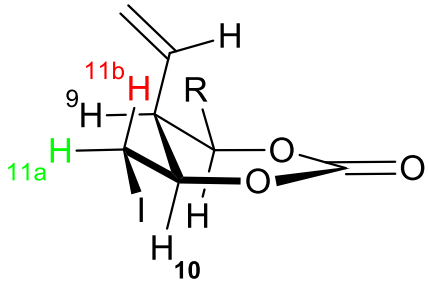


Figure 16. ^{1}H-NMR Split Pattern for H-20a and H-20b

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1.9 Discussion of Gaussian Calculations

Computational studies, using the Gaussian software package, were conducted in order to provide some insight into the possible origin of stereoselectivity of the iodocyclization reaction (converting **1.69** to **1.71**, see Scheme *27*). Optimized geometries for the R, S, R and R, R, R stereoisomers of **1.71** were obtained, and energies compared, progressing from the semi-empirical AM1 method to increasingly higher levels of theory.

Three sets of optimized molecular geometry energy minimizing calculations- AM1, HF 3-21g, and HF 6-31g- were conducted on both R, S, R and R, R, R isomers of (4R,5R,6R)-4-(2-(benzyloxy)ethyl)-6-(iodomethyl)-5-vinyl-1,3-dioxan-2-one. The final result for the R, S, R isomer was -2187664.379 kcal/mol. and for the R, R, R isomer was -2187662.486 kcal/mol., an energy difference of 1.89 kcal/mol.

Higher level DFT B3LYP (6-31g (d, p) for C, H, O; LANL2DZ for I) calculations were conducted on smaller carbonates (methyl replacing $BnOCH_2CH_2$) with corresponding stereochemistry revealing slightly higher stability of the minor product. The most stable conformer of the major product, possessing an axial vinyl group, was found to be 0.18 kcal/mol less stable than the most stable conformer of the alternative diastereomer placing the vinyl group in an equatorial position (Figure 18). The isomers' energetic similarities suggest that there is no obvious energetically preferred isomer. The major product, which is the energetically less stable isomer, must be formed at a higher rate (kinetic control). The pathways for the two isomers provide insight on their production rates. The more stable, minor isomer is formed through sterically unfavorable pathway where strong steric interactions are present. Steric interactions are not present in the pathway leading to the less stable, major isomer.

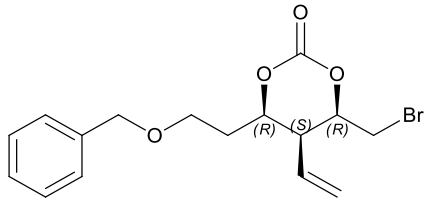


Table 12. Summary of (4R,5R,6R)-4-(2-(benzyloxy)ethyl)-6-(iodomethyl)-5-vinyl-1,3-dioxan-2-one Gaussian Calculation Results

Calculation	Energy (kcal/mol)	Dipole Moment (Debye)
AM1	-130.148	3.7932
HF 3-21G	-2178279.746	3.4626
HF 6-31G(d,p)	-2187664.379	3.5878

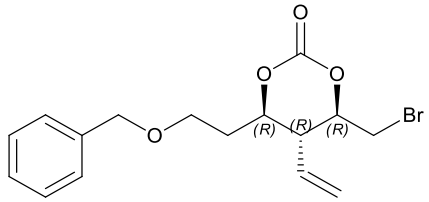


Table 13. Summary of (4R,5R,6R)-4-(2-(benzyloxy)ethyl)-6-(iodomethyl)-5-vinyl-1,3-dioxan-2-one Gaussian Calculation Results

Calculation	Energy (kcal/mol)	Dipole Moment (Debye)
AM1	-131.0412	4.2641
HF 3-21G	-2178277.275	4.4471
HF 6-31G(d,p)	-2187662.486	4.3168

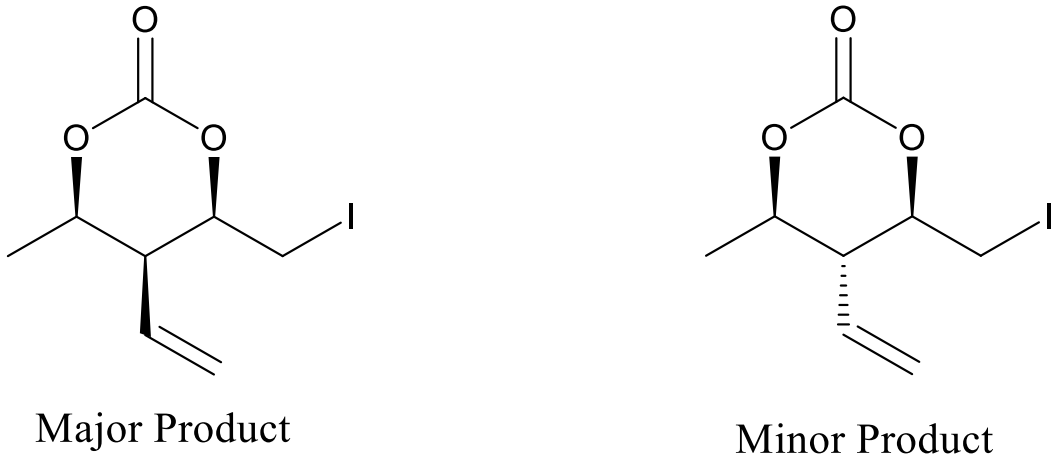
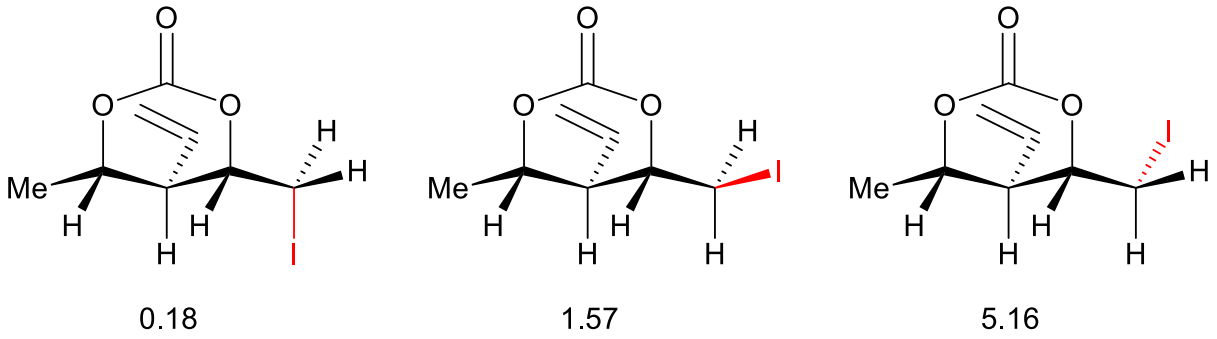


Figure 17. Smaller Carbonate Used in DFT B3LYP calculations (basis set: 6-31g (d, p) for C, H, O; LANL2DZ for I).

major product (axial vinyl group)



more stable product (equatorial vinyl group)

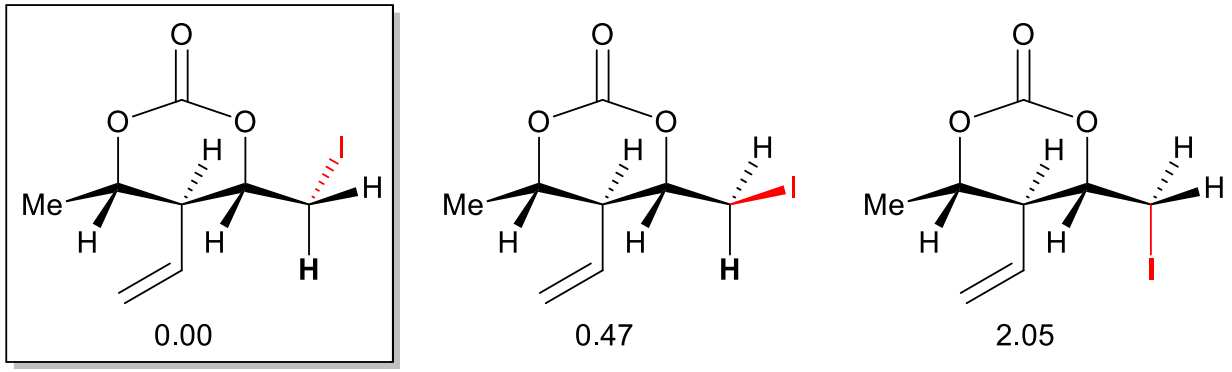
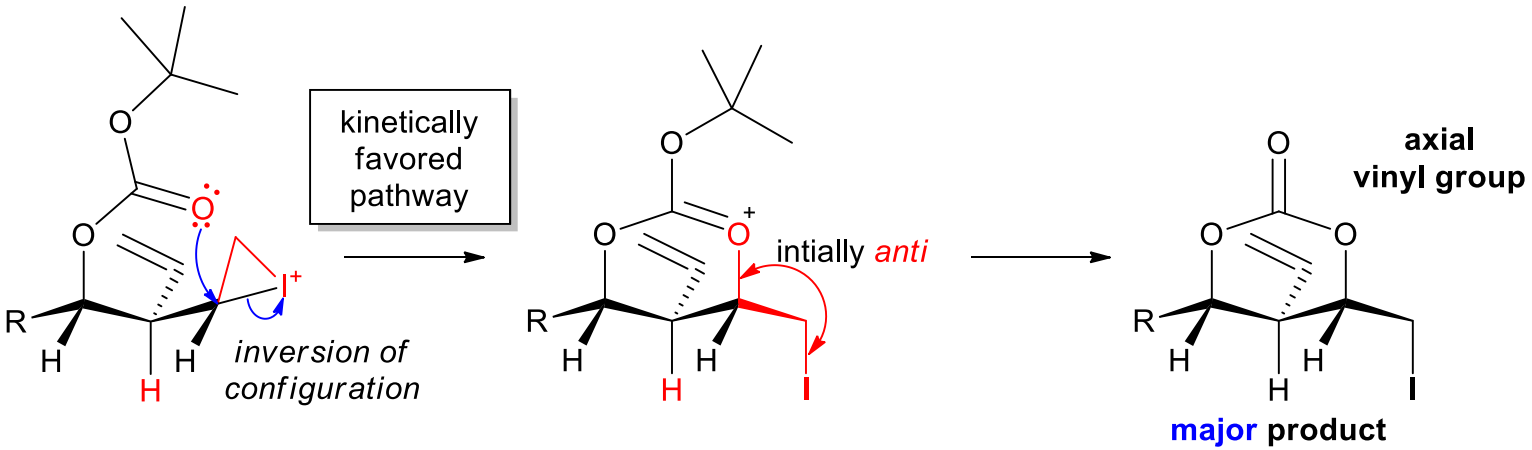
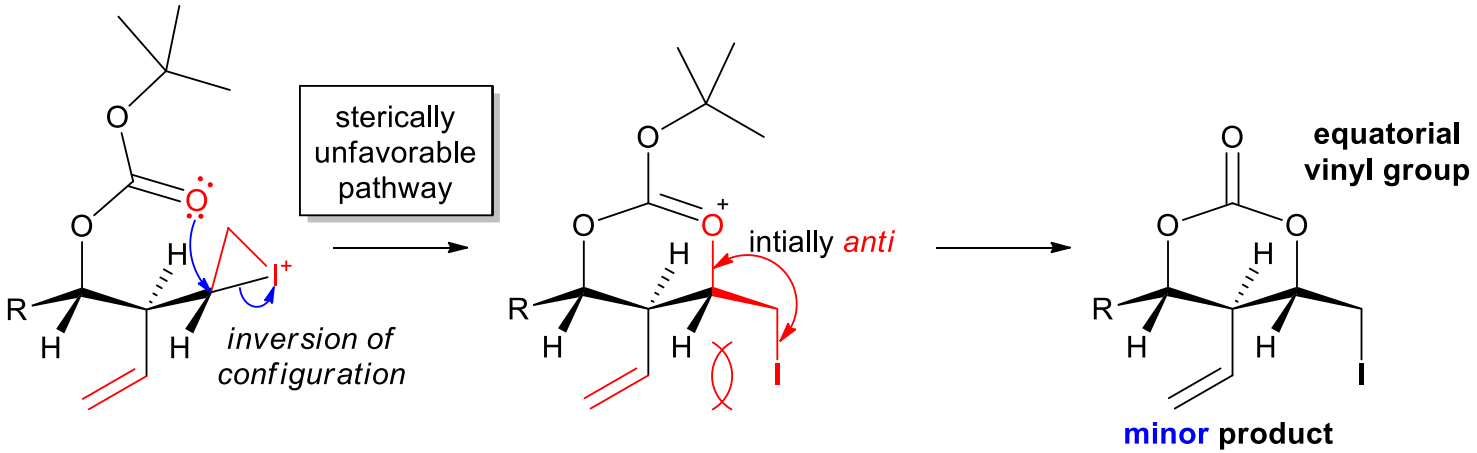


Figure 18. Relative Conformational Energies (kcal/mol) of the Smaller Carbonate.



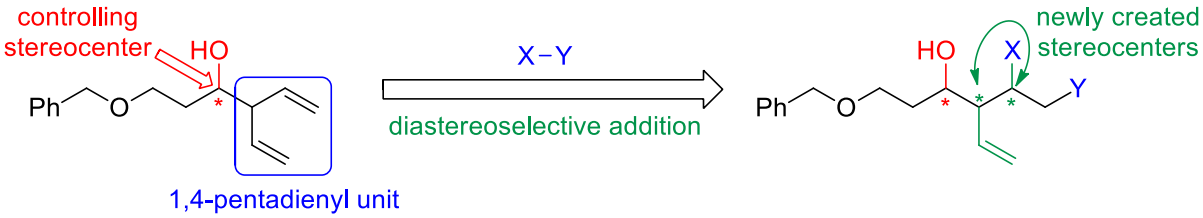
Scheme 29. Formation of Major Isomer, Sterically Favorable Pathway



Scheme 30. Formation of Minor Isomer, Sterically Unfavorable Pathway

1.10 Conclusion

Prostaglandin $PGF_2\alpha$ is a pro-inflammatory prostaglandin and synthesis of a competing PGF synthase substrate could be used to control inflammation. As part of our $PGF_2\alpha$ synthesis, 1-(benzyloxy)-4-vinylhex-5-en-3-ol was synthesized. Our goal was to use the alcohol stereocenter to control the diastereoselective functionalization (desymmetrization) of the 1,4-pentadienyl unit to generate two stereocenters adjacent to the original hydroxyl stereocenter (Scheme 31).



Scheme 31. Diastereoselective Functionalization (Desymmetrization) of the 1,4-Pentadienyl Unit

Iodocyclization was used to desymmetrize the 1,4-pentadienyl unit via addition of an iodine electrophile and oxygen nucleophile across one of the vinyl groups of the unit. Before synthesizing 4-(2-(benzyloxy)ethyl)-6-(iodomethyl)-5-vinyl-1,3-dioxan-2-one, 4-(iodomethyl)-6-methyl-1,3-dioxan-2-one, a model system was developed and synthesized. Initially a carbamate iodocyclization was attempted; however, due to difficulties with carbamate iodocyclization product stability, the synthetic pathway was abandoned. An alternative using carbonate iodocyclization was explored and found to be successful.

Our target compound 4-(2-(benzyloxy) ethyl)-6-(iodomethyl)-5-vinyl-1,3-dioxan-2-one (65% yield) was synthesized with R, S, R (and S, R, S) relative stereochemistry at carbons 8, 9, and 10. The reaction proceeded with very high stereoselectivity. Structure and stereochemistry were confirmed via COSY and HSQCDEPT. Gaussian calculations (DFT B3LYP (6-31g (d, p) for C, H, O; LANL2DZ for I)) were conducted to provide relative conformation energies used to

determine a possible mechanism. The lowest energy conformation of our major product was found to be less stable than lowest energy conformer of the alternative diastereomer epimeric at the carbon bearing the vinyl group. This suggest that the reaction proceeds through a kinetically controlled mechanism, with the less stable isomer being formed at a higher reaction rate.

1.11 Experimental and Spectroscopic Data

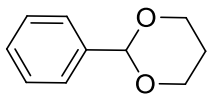
General Experimental: All solvents used were distilled, obtained from a solvent still, or HPLC grade unless otherwise noted. All purifications were carried out using flash chromatography with spherical silica gel standard or premium R_f 100 A 75-200 um, unless otherwise noted. All glassware was flame dried under nitrogen except for ozonolysis experiments. All melting points were reported at the temperature the crystal begins to melting.

Nuclear magnetic resonance (NMR) experiments were conducted using one of the following nuclear magnetic resonance spectrometers: Bruker AV-4, 400 MHz with BBI with z-gradient, QNP (1H, 19F, 13C, 31P) probes were used for samples run at 400 MHz and 100 MHz; Bruker DPX-250, 250 MHz with QNP (1H, 19F, 13C, 31P) probes were used for samples labeled 250 MHz or 62.5 MHz. MestreNova, Version: 7.1.0-9185-10.0.2-15465, © 2011-2015 Mestrelab Research S.L. and Bruker TopSpinTM were used to process all NMR spectra.

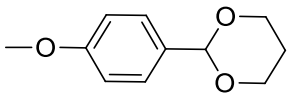
All Fourier transform infrared spectroscopy (FT-IR) experiments were conducted using a Bruker Tensor 27 FTIR with DTGS detector, mid IR source (4000 to 400 cm^{-1}), KBr beam splitter, and OPUS data collection Program. FT-IR data were processed using Essential FTIE v3.00.031 and Microsoft Office Excel 2015.

All gas chromatography mass spectrometry experiments were conducted using a CP 3800 Varian gas chromatograph with electron multiplier voltage at 1900 volts and ion trap detector. Samples were auto injected onto a splitless injector onto a DB5-MS Agilent J & W column, 5% phenol methyl siloxane. The injector temperature was 250 ^{o}C. The temperature ramp was 15 ^{o}C per minute. The mass range was 40 m/z to 650 m/z. All GCMS data were processed using System Control Varian Saturn 2200 software. All ESI experiments were conducted on a TOF/Q-TOF Mass Spectrometer. The ion source was dual ESI TOF. The mass range was 110-3000. The gas

temperature was 325°C. The gas flow was 8 L/min. The nebulizer was 20 psi. The solvent ratio was 10%, 0.1% formic acid in water and 90%, 0.1% formic acid in acetonitrile.

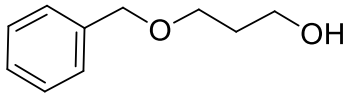


2-Phenyl-1, 3-dioxane, Benzaldehyde (20.8 g, 0.196 mol), 1,3-propanediol (14.9 g, 0.196 mol), and *p*-toluenesulfonic acid monohydrate (37 mg, 1.94 mmol) and toluene (200 mL) were added to a 500 mL round bottom flask. The mixture was refluxed for 15 h and a Dean-Stark trap was used to collect water. The mixture was washed with water and extracted with diethyl ether (3 x 200 mL). The organic portions were dried with $MgSO_4$, filtered, and the solvent removed. The product was a white, crystalline solid. Note: Small amounts of unreacted benzaldehyde are present in NMR spectra. Product, 28.1 g, was isolated giving 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.1 Hz, 2H), 7.37 (m, 7.43-7.34 3H), 5.52 (s, 1H), 4.30 (dd, *J* = 11.4, 5 Hz, 2H), 4.00 (t, *J* = 11.2 Hz, 2H), 2.26 (*J* = 12.7, 6.3 Hz, 1H), 1.47 (d, *J* = 13.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.7, 128.8, 128.2, 126.0, 101.6, 67.4, 25.8. GC/MS [M-1] m/z163.

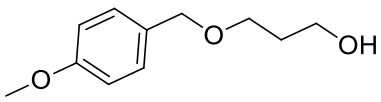


2-(4-Methoxyphenyl)-1,3-dioxane, 4-Methoxybenzaldehyde (5 g, 36 mmol), 1,3-propanediol (2.65 mL, 36 mmol), p-toluenesulfonic acid monohydrate (69 mg, 0.363 mmol) and toluene (50 mL) were placed in 250 mL round bottom flask equipped with a Dean-Stark trap. The reaction was refluxed for 15 h. The mixture was extracted with diethyl ether and washed with water. The organic portions were dried with $MgSO_4$, filtered, and solvent removed to afford white crystals (6.0 g, 84%), m.p. 40.0 °C. Note: Small amounts of ethyl acetate, hexanes, and unreacted 4-methoxybenzaldehyde are present in the NMR spectra. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43(d, *J* =

9.1 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 5.46 (s, 1H), 4.25 (dd, *J*=10.5, 5.0 Hz, 2H), 3.98 (td, *J* = 12.4, 2.5 Hz, 2H), 3.80, (s, 3H), 2.26-2.17 (m, 1H), 1.45-1.38 (m, 1H). GC/MS [M-1] m/z193

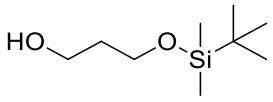


(3-Benzyloxy)propan-1-ol, 2-Phenyl-1,3-dioxane (10 g, 60 mmol) was added to a 500 mL dry 3-neck flask. BH_3-THF (1 M) (350 mL) was added dropwise from an addition funnel and the mixture was allowed to stir at room temperature overnight. The mixture was cooled to 0 ^oC and quenched with distilled ice water. Organics were extracted with ethyl acetate dried over $MgSO_4$, filtered and solvent removed. Crude product was a clear oil. (7.7 g, 77%) Purification was effected by flash chromatography eluting with 95% hexanes/ 5% ethyl acetate. Note: Small amounts of unreacted 2-Phenyl-1, 3-dioxane are present in NMR spectra. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 5H), 4.53 (s, 2H), 3.78 (t, *J* = 5.7 Hz, 4H), 3.67 (t, *J* = 5.8 Hz, 2H), 2.35 (s, 1H), 1.89 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1, 128.4, 127.6, 73.1, 69.1, 61.8, 32.1 MS (ESI^+) 175.0 V. [M] 166.1 m/z.

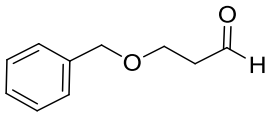


3-(4-Methoxybenzyloxy)propanol, Borane in THF (1M, 80 mL, 80 mmol) was added to a 250mL three neck round bottom flask. 2-(4-methoxyphenyl)-1,3-dioxane (3 g, 0.155 mmol) was added at 0 ^oC. The reaction was warmed to room temperature and stirred overnight. The mixture was cooled to 0 ^oC, quenched with water, extracted with diethyl ether (3 x 80 mL) and then washed with water. The organic portions were dried with $MgSO_4$, filtered, and solvent was removed. Purification was effected by flash chromatography, 90% hexanes 10% ethyl acetate, increasing polarity to 75% ethyl acetate 25% hexanes. Product was isolated as a clear light yellow oil (2.9 g, 95%). ^1H NMR

(400 MHz, $CDCl_3$) δ 7.25 (t, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 4.56 (s, 1H), 4.43 (s, 1H), 3.78 (s, 3H), 3.73 (t, *J* = 5.7, Hz, 2H), 3.60 (t, *J* = 5.8 Hz, 2H), 2.70 (d, 1H), 1.83 (t, 2H). GC/MS [M] 196m/z, [$C_8H_9O^+$] 121m/z



3-((*tert*-Butyldimethylsilyl)oxy)propan-1-ol, (3-bromopropoxy)(tert-butyl)dimethylsilane (1 g, 3.95 mmol) and KOH (0.222 g, 3.95 mmol) were added to DMF (20 mL) and water (2 mL) in a 50 mL round bottom flask. The reaction was allowed to stir for 6 h. Mixture was diluted with water and extracted with diethyl ether, dried with $MgSO_4$, filtered, and solvent removed. Purification was effected by flash chromatography, eluting with 90% dichloromethane/ 10% methanol. Solvent was removed by vacuum. Product was a clear oil; 0.47 g, was isolated for a 63% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (t, *J* = 5.7 Hz, 2H), 3.51 (t, *J* = 6.5 Hz, 2H), 2.09-1.98 (m, 2H), 0.90 (s, 9H), 0.07 (s, 6H). ^{13}C NMR 60.4, 34.6, 31.6, 25.9, 18.7, -5.1.



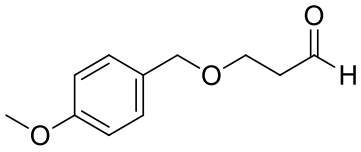
Method A

(3-Benzyloxy) propanal, PCC (12.9 g, 60 mmol) was added to 500mL of CH_2Cl_2 in a 1 L round bottom flask. Al_2O_3 (12.9 g, weight eq. of PCC) was added to solution, and the mixture was allowed to stir for 30 min. (3-Benzyloxy) propan-1-ol (5 g, 30 mmol) was then added. The reaction was allowed to run for one day. The color changed to a dark, almost black. Solids were filtered through a fritted filter topped with silica gel. Purification was effected by flash chromatography,

eluting with 90% hexanes 10% ethyl acetate. Solvent was removed by vacuum. Product, (2.6 g, 52%) was isolated as a light yellow oil.

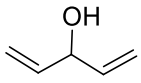
Method B

(3-Benzyloxy)propan-1-ol, (1 g, 6.02 mmol) was placed in a 100 mL round bottom flask. Toluene (14 mL) and $NaHCO_3$ (1.678 g, 20 mmol) were added and allowed to stir for 45 min. Iodine (3.38 g, 27 mmol) was added followed by TEMPO (0.104 g, 0.607 mmol). The mixture was allowed to stir for 16 h then cooled to 5 ^oC. Ethyl acetate (3.46 mL) was added to dilute the mixture. Na_2SO_3 (692 mg, 4.87 mmol) was added to quench reaction. The mixture was washed with sat. K_2CO_3 followed by brine. The organic portions were dried with Na_2SO_4, filtered, and solvent removed. Purification was effected by flash chromatography, eluting with 75% hexanes/ 25% ethyl acetate. The product, (0.53 g, 53%) was isolated as a light yellow or clear oil. Note: Small amount of ethyl acetate and hexanes are present in NMR spectra. ^1H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.34 (m, 5H), 4.54 (s, 2H), 3.82 (t, *J* = 6.2 Hz, 2H), 2.71 (d, *J* = 6.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.7, 128.4, 127.7, 73.2, 65.2, 34.

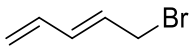


3-(4-Methoxybenzyloxy)propanal, PCC (5.5 g, 0.255 mmol) and Al_2O_3 (11 g double mass. of PCC) were added to CH_2Cl_2 (300 mL) in a 1 L round bottom flask. The solution stirred for 30 min. 3-(4-methoxybenzyloxy)propan-1-ol (2.50 g, 0.127 mmol) was added. After 4 h, the suspension was filtered through silica. Purification was effected by flash chromatography 90% hexanes 10% ethyl acetate then increased to 75% hexanes/ 25% hexanes. Product was isolated as a yellow oil at

1.31 g for a 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.86 (d, *J* = 8.7 Hz, 2H), 7.02 (d, *J* = 8.7 H, 2H), 3.89 (s, 3H), 3.80 (s, 3H) 3.73 (t, *J* = 6.3 Hz 2H), 2.66 (t, *J* = 6.3 Hz 2H).

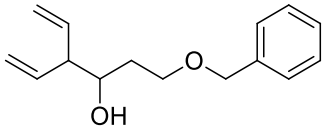


Penta-1,4-dien-3-ol, THF and ether (4:1 ratio) was added to a dry round bottom flask at 15 ^{o}C. Vinyl magnesium bromide (12.96 g, 0.857 mmol) and acrolein (4 g, 0.714 mmol) were added to reaction. The mixture was stirred for 3.5 h, and then quenched with saturated ammonium chloride (¼ reaction solvent volume) at 0 ^{o}C. The precipitate was removed by filtration. The solution was extracted ethyl acetate, dried with $MgSO_4$, and filtered. Purification was effected by flash chromatography 75% ethyl acetate/ 25% hexanes. Solvent was removed by vacuum to afford to afford product (3.79 g, 63%) as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.93-568 (m, 2H), 5.24-.08 (m, 4H), 4.51 (t, *J* = 5.8 Hz 1H), 3.00 (s, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 139.1, 115.0, 73.7.

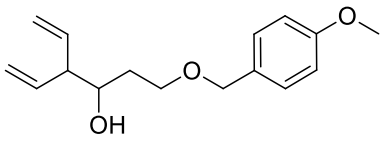


(E)-5-Bromopenta-1, 3-diene, Penta-1,4-dien-3-ol (1.99 g, 24. mmol) was added to a 25 mL round bottom flask followed by hexanes (5 mL). Temperature was lowered to -50^{o}C. HBr (48% aqueous solution, 5.3 mL) was added dropwise. The mixture was stirred for 22 h. Saturated sodium bicarbonate (until mixture stopped bubbling) was added to neutralize the reaction. The organics were extracted ethyl acetate (3 x 50 mL), dried with $MgSO_4$, and filtered. Solvent was removed by vacuum and the residue was purified was effected by flash chromatography eluting with 10% ethyl acetate/ 90% hexanes. Product, (2.8 g, 81) was isolated as a light yellow oil. Note: A small amount of unreacted penta-1,4-dien-3-ol is present in NMR spectra. ^{1}H NMR (400 MHz, $CDCl_3$)

δ 6.48-6.22 (m, 2H), 6.05-5.79 (m, 1H), 5.47-5.10 (m, 2H), 4.04 (s, 2H). GC/MS [$C_5H_4^+$] 67m/z, [$C_4H_9Br^+$] 132

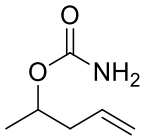


1-(Benzyloxy)-4-vinylhex-5-en-3-ol, (3-benzyloxy)propanal (0.1 mg, .661 mmol) and (E)-5-bromopenta-1,3-diene (97 mg, 0.166 mmol) were added to a dry round bottom flask. The flask was then cooled to -30 ^oC. DMF (10 mL) was added followed by In powder (76 mg, 0.666 mmol). The reaction was allowed to run overnight, then quenched with water, diluted with brine, extracted with ethyl acetate (3 x 50 mL), dried with $MgSO_4$, filtered and solvent removed. Purification was effected by flash chromatography 95% hexanes 5% ethyl acetate. Product (48 mg, 32%) was isolated as a very light yellow oil. Note: Small amounts of ethyl acetate, hexanes and benzaldehyde are present in NMR spectra. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.29 (m, 5H), 5.97-5.78 (m, 2H), 5.21- 5.08 (m, 4H), 4.53 (s, 2H), 3.88-3.79 (m, 2H), 3.78-3.63 (m, 2H), 2.88-2.77 (m, 1H), 1.90-1.69 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0, 137.6, 137.1 128.4 127.7, 117.0, 116.7, 73.3, 72.6, 68.9, 54.7, 33.9. GCMS $C_{15}H_{20}O_2$ [M] 232.7

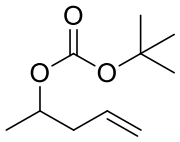


1-(4-Methoxybenzyloxy)-4-vinylhex-5-en-3-ol 1.55, In powder (0.649 mg, 5.65 mmol) was added to a 100 mL round bottom flask. The flask was then cooled to 0^oC and DMF (50 mL), 3-(4-methoxybenzyloxy)propanal (0.1 mg, 5.15 mmol), and (E)-5-bromopenta-1,3-diene (0.162 mg, 1.1 mmol) were added. The reaction was allowed to run for 4 h at 0 ^oCthen quenched with water.

The solution was extracted with diethyl ether, dried with $MgSO_4$, and solvent removed. Purification was effected by flash chromatography 85% hexanes 15% ethyl acetate then increase to 75% hexanes/ 25% ethyl acetate. Product, 0.42 mg, was isolated as a light yellow oil for a 31% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.2 Hz 2H), 6.88 (d, J = 8.2 Hz 2H), 5.86 (m, 2H), 5.13 (m, 4H), 4.45 (s, 2H), 3.80 (s, 3H) 3.68 (m, 2H), 2.88 (m, 1H), 2.81 (m,1H), 1.78 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.7, 137.2, 130.1, 129.3, 116.9, 116.7, 113.8, 72.9, 68.7, 55.3, 54.8, 33.9.

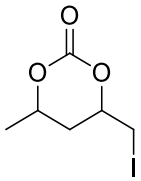


Pent-4-en-2-yl carbamate. To a solution of 4-penten-2-ol (0.5 g, 5.8 mmol) in 8.3 mL of chloroform was added dropwise over 30 min to a solution of trichloroacetyl isocyanate (1.1 g, 5.8 mmol) in 2.5 mL of chloroform in a 25 mL round bottom flask cooled to 0 ^{o}C. After 10 min K_2CO_3 (0.8 g, 5.78 mmol) in a mixture of 4.5 mL of methanol and 3 mL water, was added to the reaction mixture. The mixture was allowed to stir for 4 h at 0 ^{o}C, then warmed to rt for 2 h. The mixture was acidified to pH 6 with 0.5 M H_2SO_4. Organics were extracted three times with chloroform, dried with $MgSO_4$, filtered, and solvent removed *in vacuo*. The product (0.73 g, 98%) was a white, crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (m, 1H), 5.08 (m, 2H), 4.85 (m, 1H), 4.65 (s, 2H), 2.29 (m, 2H), 1.23 (d, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6, 133.7, 117.6, 70.8, 40.4, 19.6.



***Tert*-butyl pent-4-en-2-yl carbonate,**[7] 4-Penten-2-ol (0.1 g, 1.16 mmol) was added to 15 mL of CH_2Cl_2 cooled to 0°C. Di-*tert*-butyl dicarbonate (0.38 g, 1.74 mmol), Et_3N (0.047 g, 0.464 mmol), and 4-(dimethylamino)pyridine (0.02 g, 0.023 mmol) were added at room temperature. The reaction was allowed to stir for 10 hr. The mixture was diluted with CH_2Cl_2 and water. Organics were dried over $MgSO_4$, filtered, and solvent removed *in vacuo*. Purification $AgNO_3$ 10 wt% on silica 100% hexanes increased to 97% hexanes/ 3% ethyl acetate. The product is a clear oil (32 mg 15%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (ddt, J = 15.0, 10.1, 7.2 Hz, 1H), 5.16 – 5.03 (m, 2H), 4.86 – 4.69 (m, 1H), 2.40 (dt, J = 13.3, 6.5 Hz, 1H), 2.36 – 2.22 (m, 1H), 1.48 (s, 4H), 1.47 (s, 1H), 1.27 (dd, J = 6.4, 4.6 Hz, 3H), 0.07 (s, 1H).

Pen-4-en-2-ol (0.5 g, 5.8 mmol) was added to dry diethyl ether. In a separate flask, Boc-ON (1.43 g 5.8 mmol) was added to dry THF. *n*-BuLi 1M in hexanes (5.8mL, 5.8 mmol) was added dropwise to pen-4-en-2-ol solution at -78 °C and allowed to stir for 30 min. The mixture was quickly transferred to the Boc-ON solution at 0 °C and allowed to stir for four hours. The mixture was then washed with 2 N NaOH twice and brine once. The organics were extracted with ether and dried of $MgSO_4$. The crude product is light yellow oil (0.96 g, 89%)

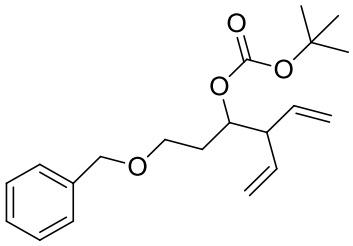


4-(iodomethyl)-6-methyl-1,3-dioxan-2-one,[25] *Tert*-butyl pent-4-en-2-yl carbonate (.054 g, 2.9 mmol) was added to 15 mL of CH_3CN in a 25 mL round bottom flask at 0 °C. NIS (1.3 g, 5.8 mol). The reaction was allowed to stir for 9 h at 4 °C. The reaction was quenched with saturated NaS_3O_2 and saturated $NaHCO_3$. Organics were extracted with CH_2Cl_2 twice and dried over $MgSO_4$. Initial

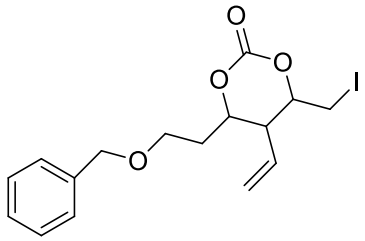
purification: flash chromatography 90:10 ethyl acetate: hexanes with 10% ethyl acetate increases every two column volumes. The product (.05 g, 8%) is a clear yellow oil.

Major Product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63(m, 1H), 4.47(m, 1H), 3.48(dd, 1H), 3.43(dd, dd, *J* = 10.53 4.26 Hz, 1H), 3.26(dd, *J* = 10.5, 7.6 Hz, 1H), 2.40(dt, *J* = 14.2, 3.0 Hz, 1H), 1.70((dt, *J* = 14.2, 11.6 Hz, 1H), 1.45(d, 3H).

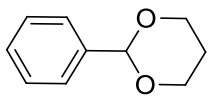
Minor Product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72(m, 1H), 4.63(m, 1H), 3.43(dd, 1H), 3.31(dd, 1H), 2.25(m, 1H), 2.14(m, 1H), 1.49(d, 3H).



1-(benzyloxy)-4-vinylhex-5-en-3-yl tert-butyl carbonate, 1-(Benzyloxy)-4-vinylhex-5-en-3-ol (0.573 g, 2.47 mmol) was added to a 50 mL round bottom flask. Acetonitrile (25 mL) was added and temperature was lowered to 0 ^{o}C. DMAP (0.30 g, 2.47 mmol), triethylamine (1.75 g, 0.173 mmol), and $(Boc)_2O$ (4.84 g, 0.222 mmol) were added and the temperature was gradually increased to room temperature. After 26 h the reaction was diluted with ethyl acetate, washed with brine, dried over $MgSO_4$, and solvent removed. Flash chromatography was conducted using 85:15 ethyl acetate: hexanes. The product, 0.4 g, was isolated as a clear oil for a 50% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 4H), 5.88 – 5.74 (m, 2H), 5.21 – 5.06 (m, 4H), 4.96 – 4.86 (m, 1H), 4.49 (s, 2H), 3.52 (q, *J* = 7.5, 6.7 Hz, 2H), 3.01 (q, *J* = 7.3 Hz, 1H), 1.89 (dddt, *J* = 43.8, 14.7, 10.3, 4.5 Hz, 2H), 1.84 (ddt, *J* = 14.7, 10.3, 5.6 Hz, 1H), 1.46 (s, 9H), ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 148.0, 138.1, 128.7, 128.0, 125.6, 124.8, 80.8, 79.0, 73.5, 65.2, 60.6, 42.6, 33.4, 21.2, 14.4, 2.1.



4-(2-(benzyloxy)ethyl)-6-(iodomethyl)-5-vinyl-1,3-dioxan-2-one, CH_3CN (5 mL) was added to a 25 mL round bottom flask. The temperature was lowered to -50 ^oC. 1-(benzyloxy)-4-vinylhex-5-en-3-yl tert-butyl carbonate (0.042 g, 0.126 mmol) and NIS (0.085 g, 0.379 mmol) were added. The reaction was allowed to stir for 1 d. The reaction was then quenched with sat. $Na_2S_2O_4$, extracted with ethyl acetate, dried with $MgSO_4$, and solvent removed. Flash chromatography was conducted using 90:10 ethyl acetate: hexanes. Product, 0.033 g, was isolated as a light yellow oil for a 65% yield. ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (ddt, *J* = 15.1, 13.2, 7.3 Hz, 5H), 5.60 – 5.50 (m, 2H), 5.47 – 5.36 (m, 1H), 4.79 (ddd, *J* = 8.0, 4.7, 2.6 Hz, 1H), 4.69 (ddd, *J* = 10.2, 4.9, 2.8 Hz, 1H), 4.57 – 4.45 (m, 2H), 3.68 (td, *J* = 9.3, 4.2 Hz, 1H), 3.58 (dt, *J* = 9.8, 5.1 Hz, 1H), 3.33 (dd, *J* = 10.0, 4.9 Hz, 1H), 3.03 (t, *J* = 10.0 Hz, 1H), 2.96 (dt, *J* = 9.8, 2.7 Hz, 1H), 1.95 (ddd, *J* = 18.6, 9.0, 4.5 Hz, 1H), 1.84 (ddt, *J* = 14.2, 9.4, 4.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 147.9, 138.0, 128.7, 128.0, 128.0, 125.5, 124.7, 80.7, 79.0, 73.5, 65.1, 42.5, 33.3, 2.1.



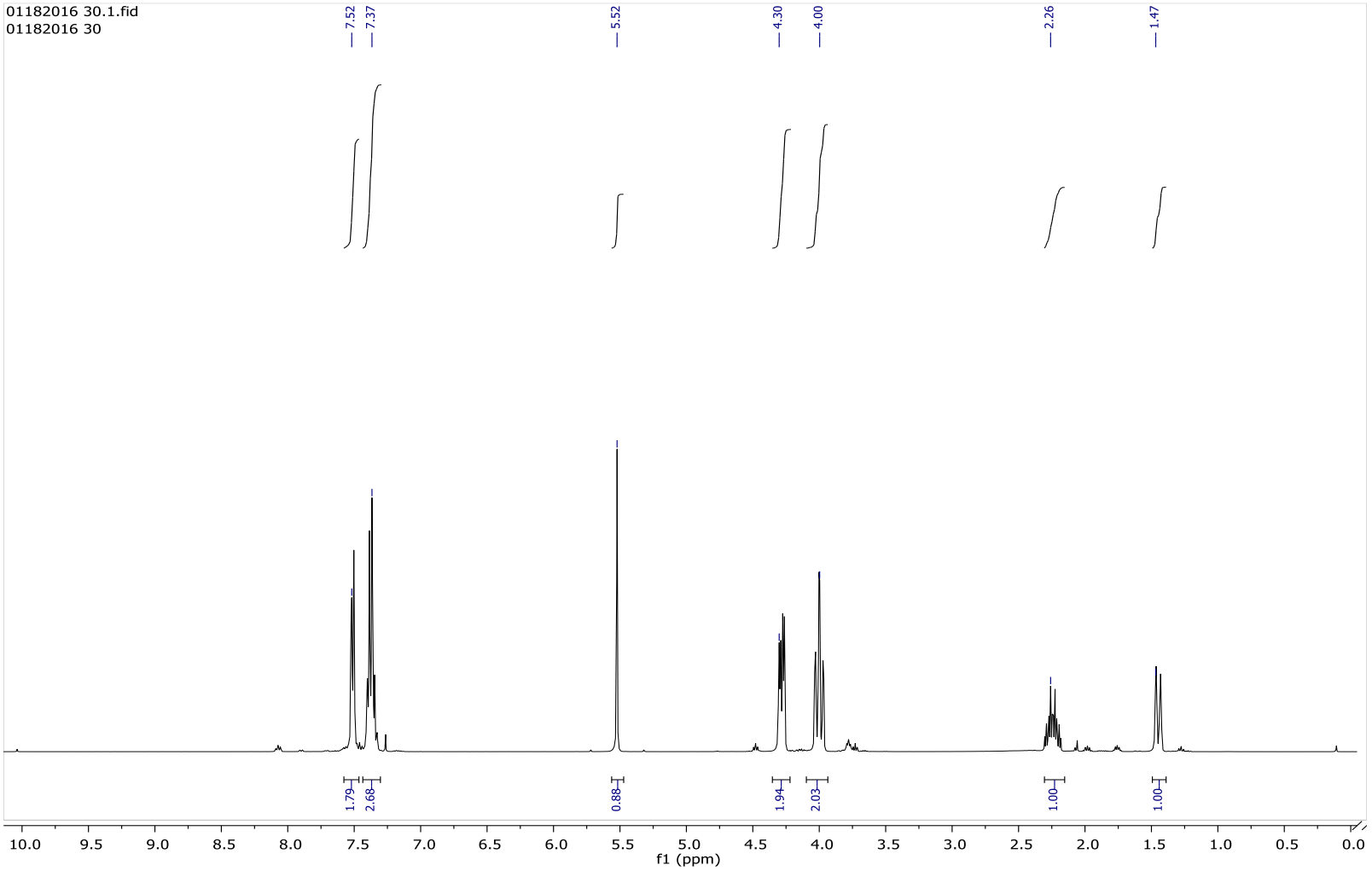
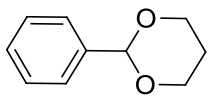


Figure 19. 2-Phenyl-1,3-dioxane ^{1}H-NMR (400MHz, $CDCl_3$)



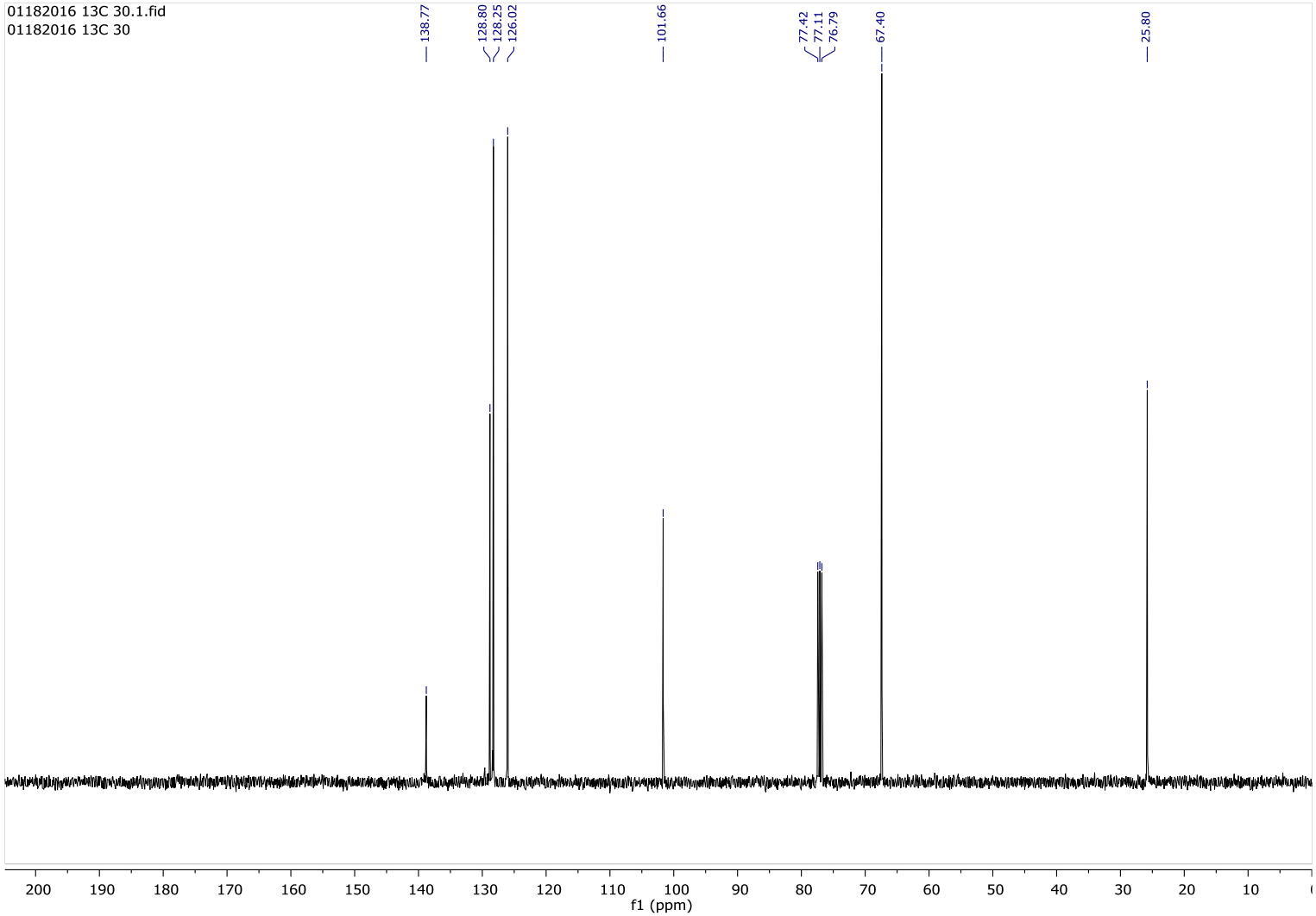
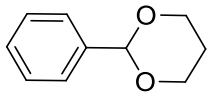


Figure 20. 2-Phenyl-1,3-dioxane ^{13}C-NMR (101Hz, $CDCl_3$)



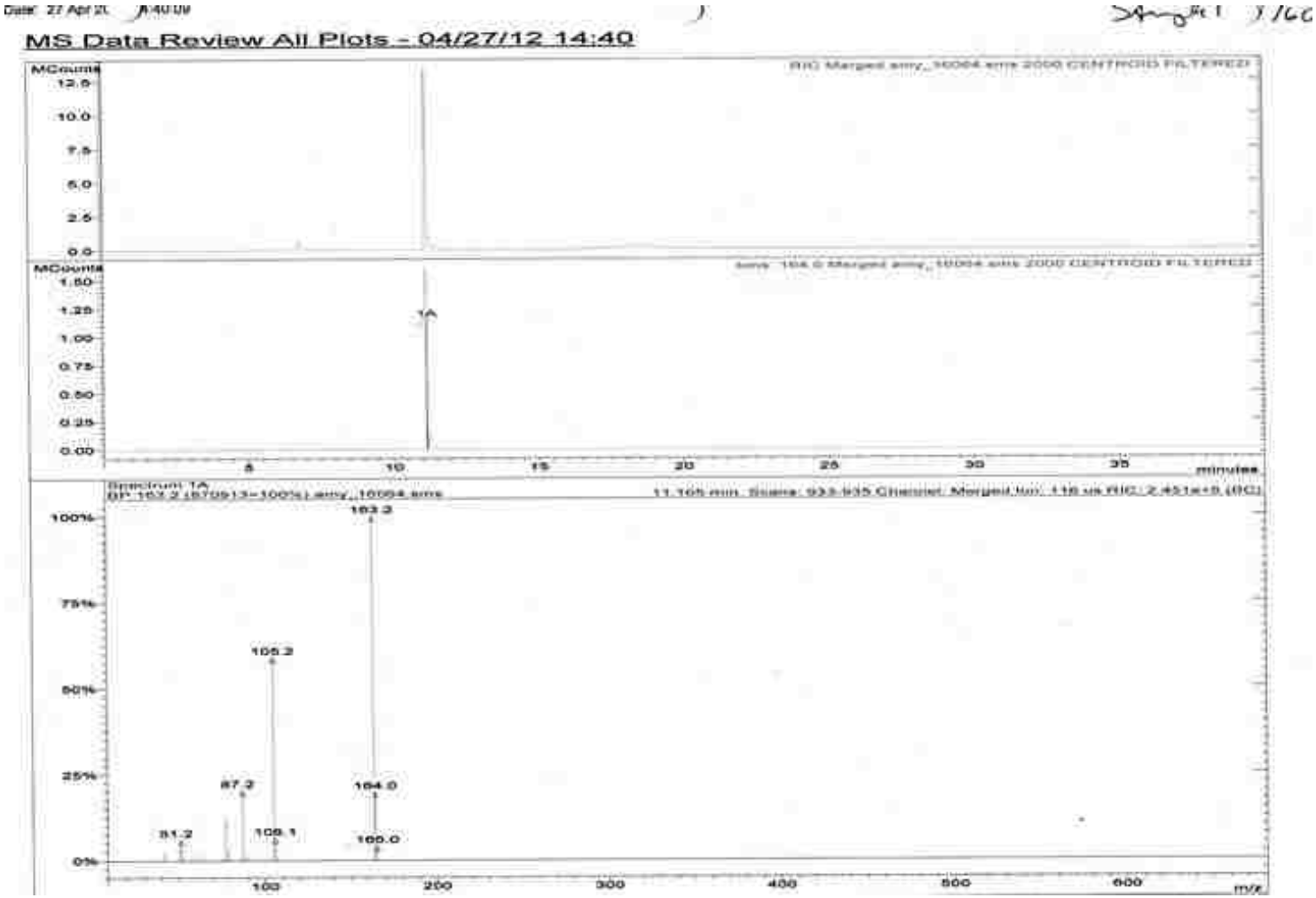


Figure 21. 2-Phenyl-1,3-dioxane, GC/MS EI (filament voltage 70 eV)

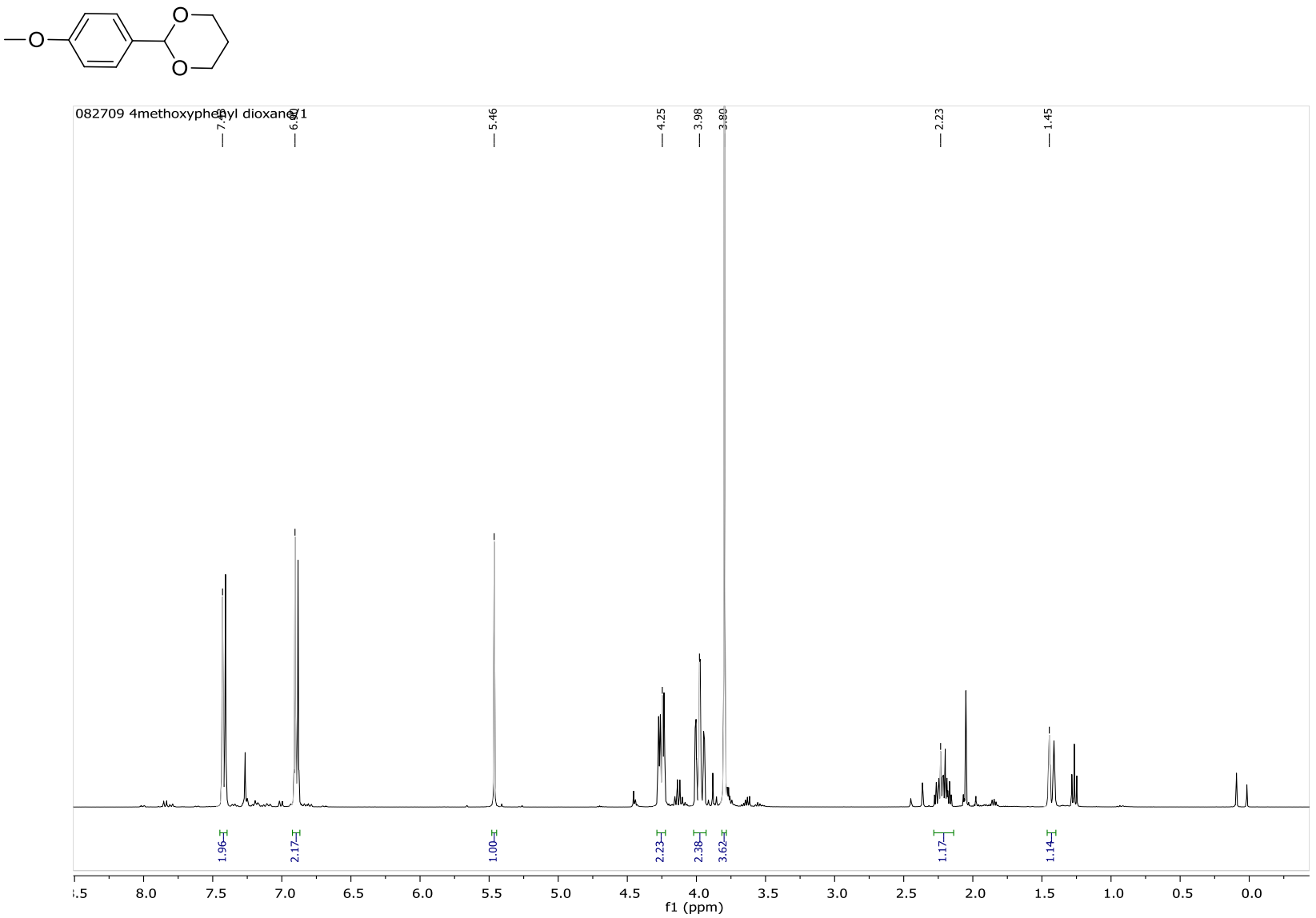


Figure 22. 2-(4-Methoxyphenyl)-1,3-dioxane, ^{1}H-NMR (400MHz, $CDCl_3$)

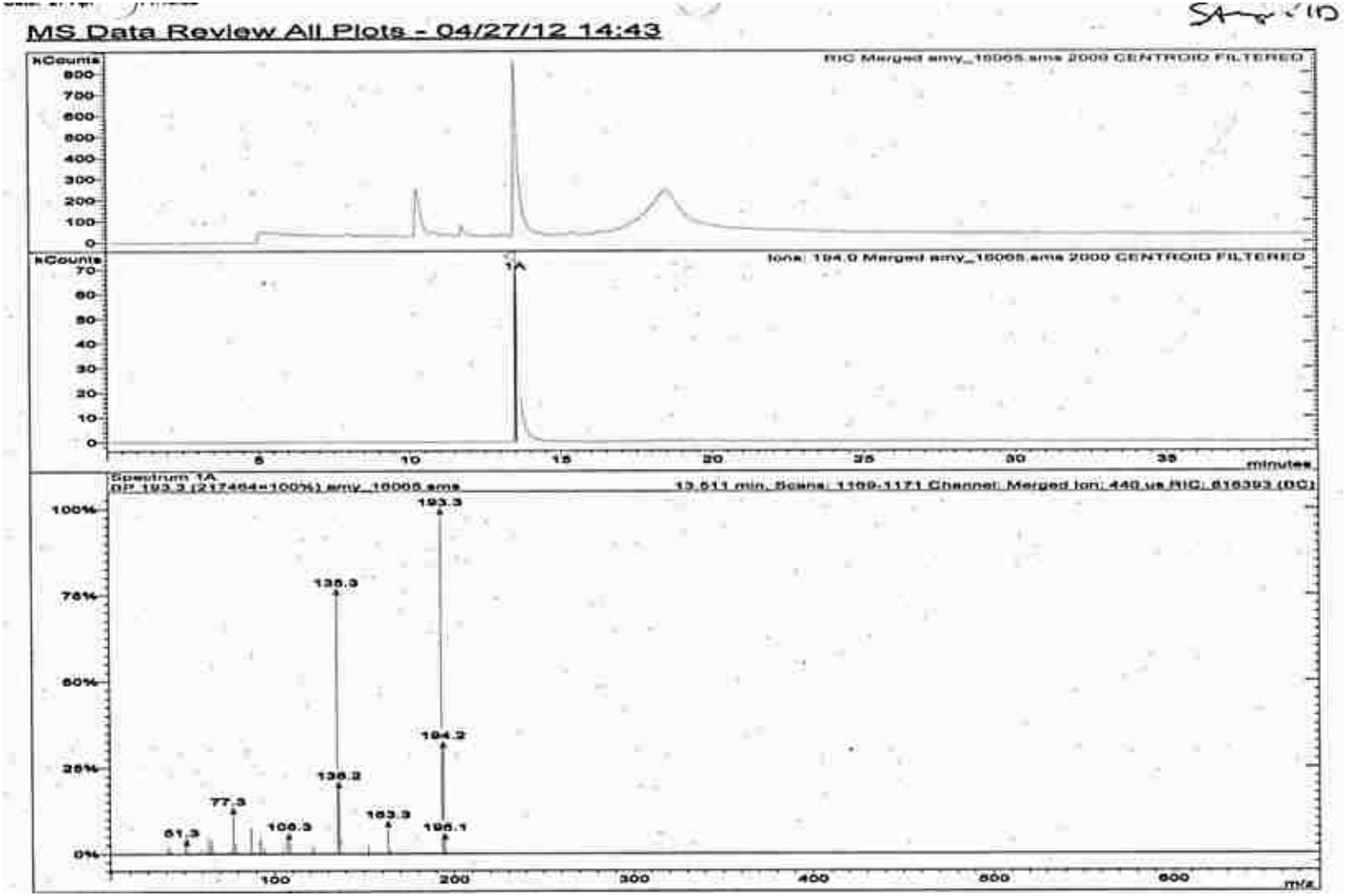


Figure 23. 2-(4-Methoxyphenyl)-1,3-dioxane, GC/MS EI (filament voltage 70 eV)

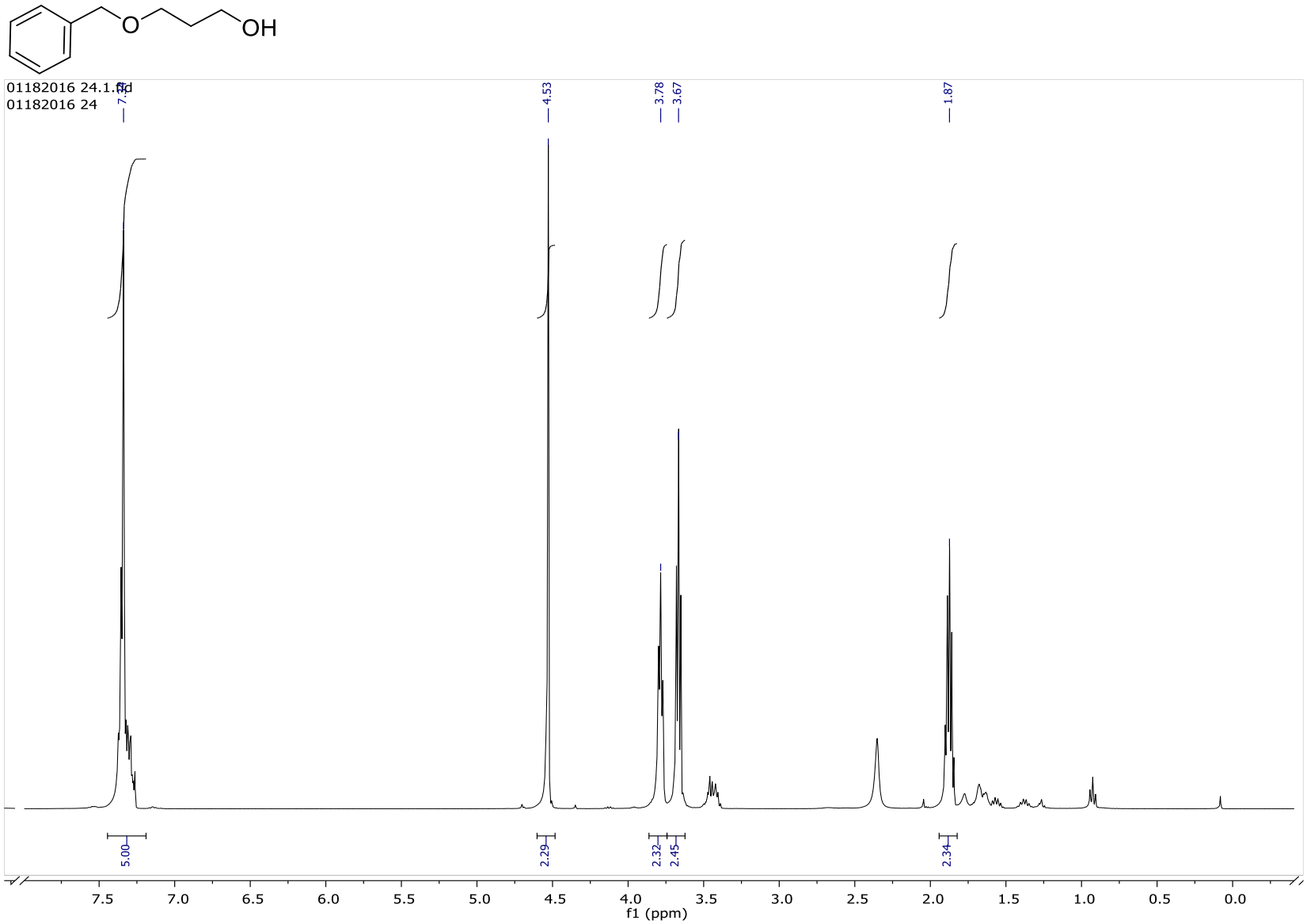
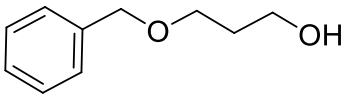


Figure 24. (3-Benzyloxy)propan-1-ol ^{1}H-NMR (400MHz, $CDCl_3$)



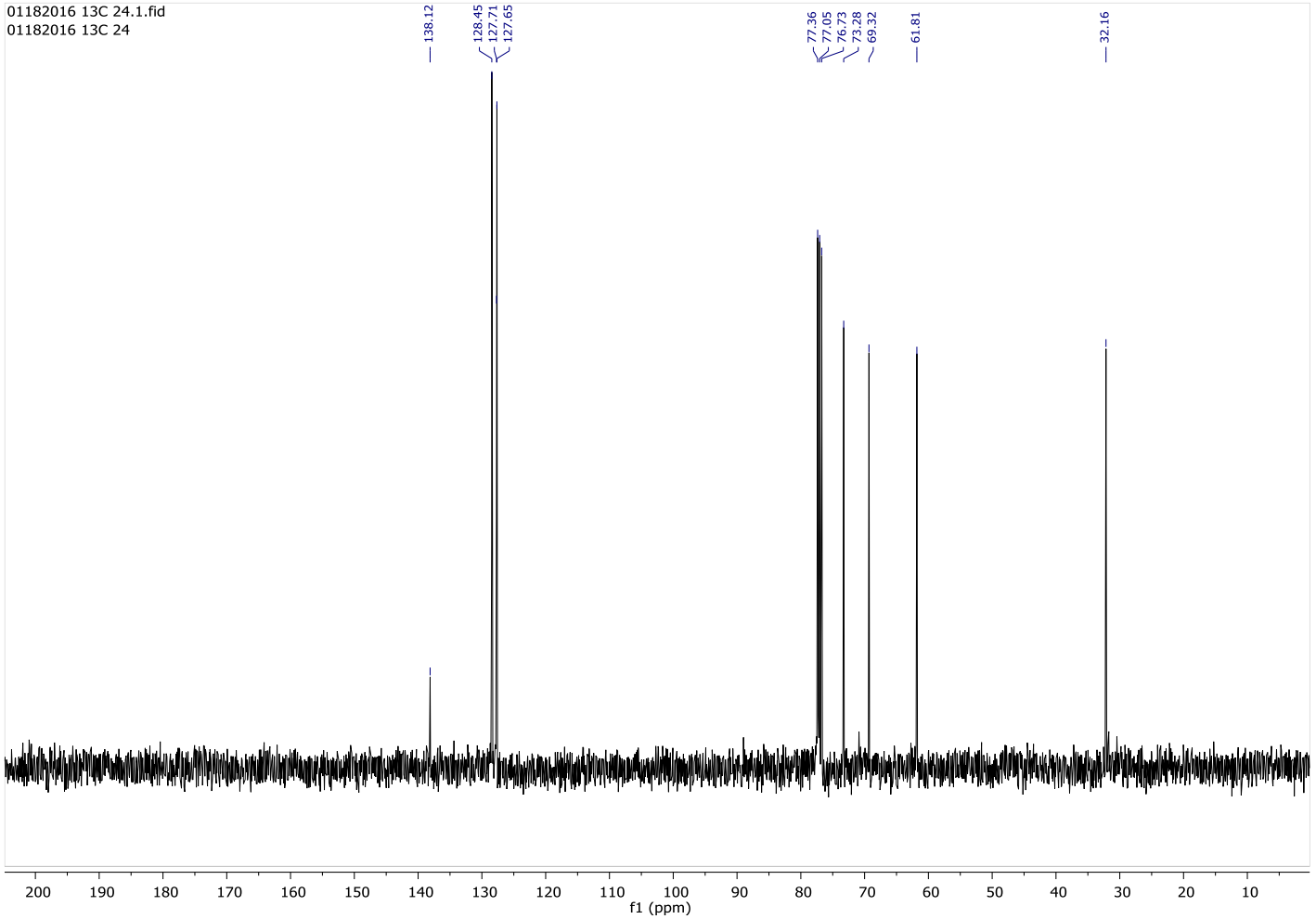
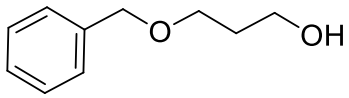


Figure 25. (3-Benzyloxy)propan-1-ol ^{13}C-NMR (101MHz, $CDCl_3$)



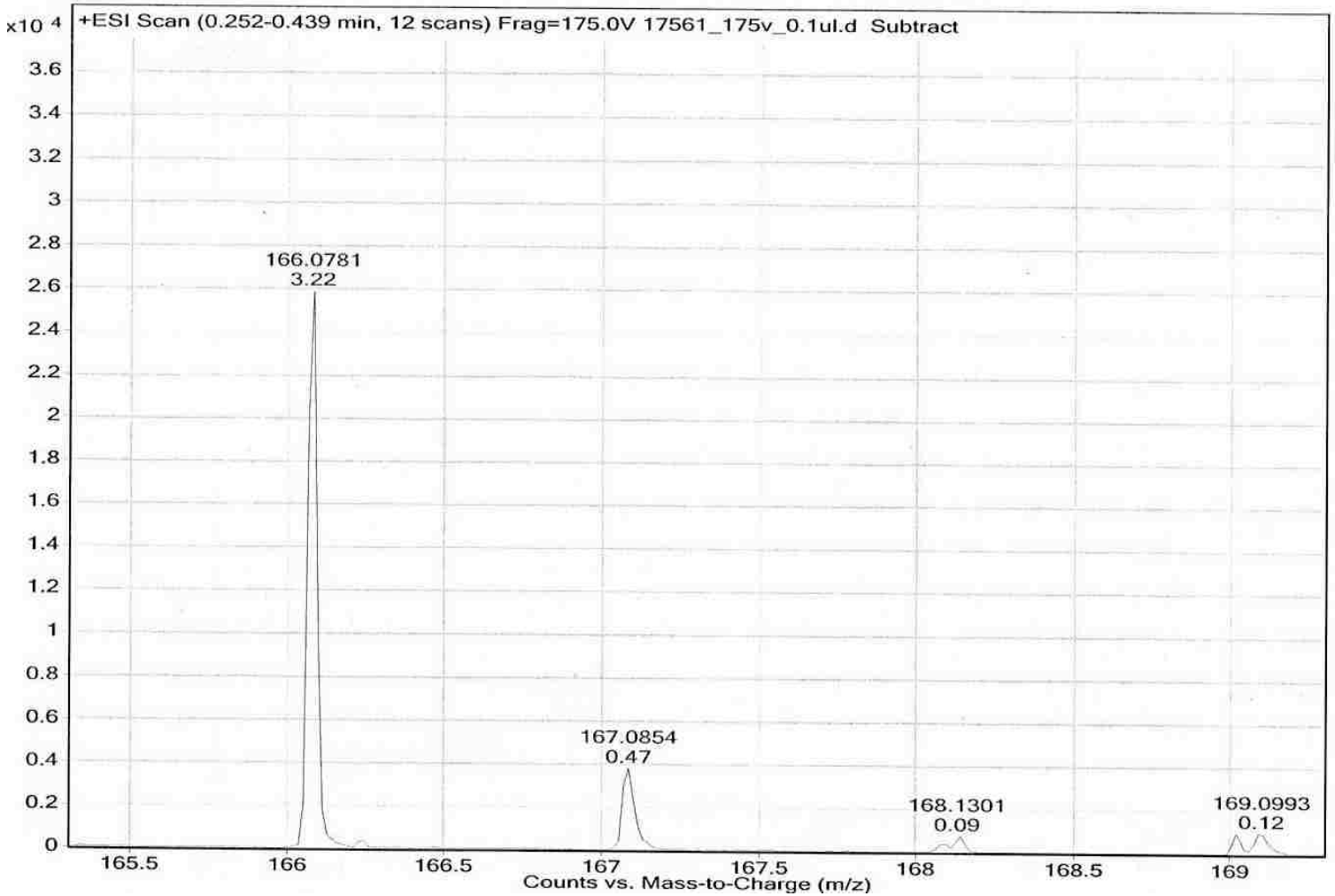


Figure 26. (3-Benzyloxy)propan-1-ol, ESI 175.0V

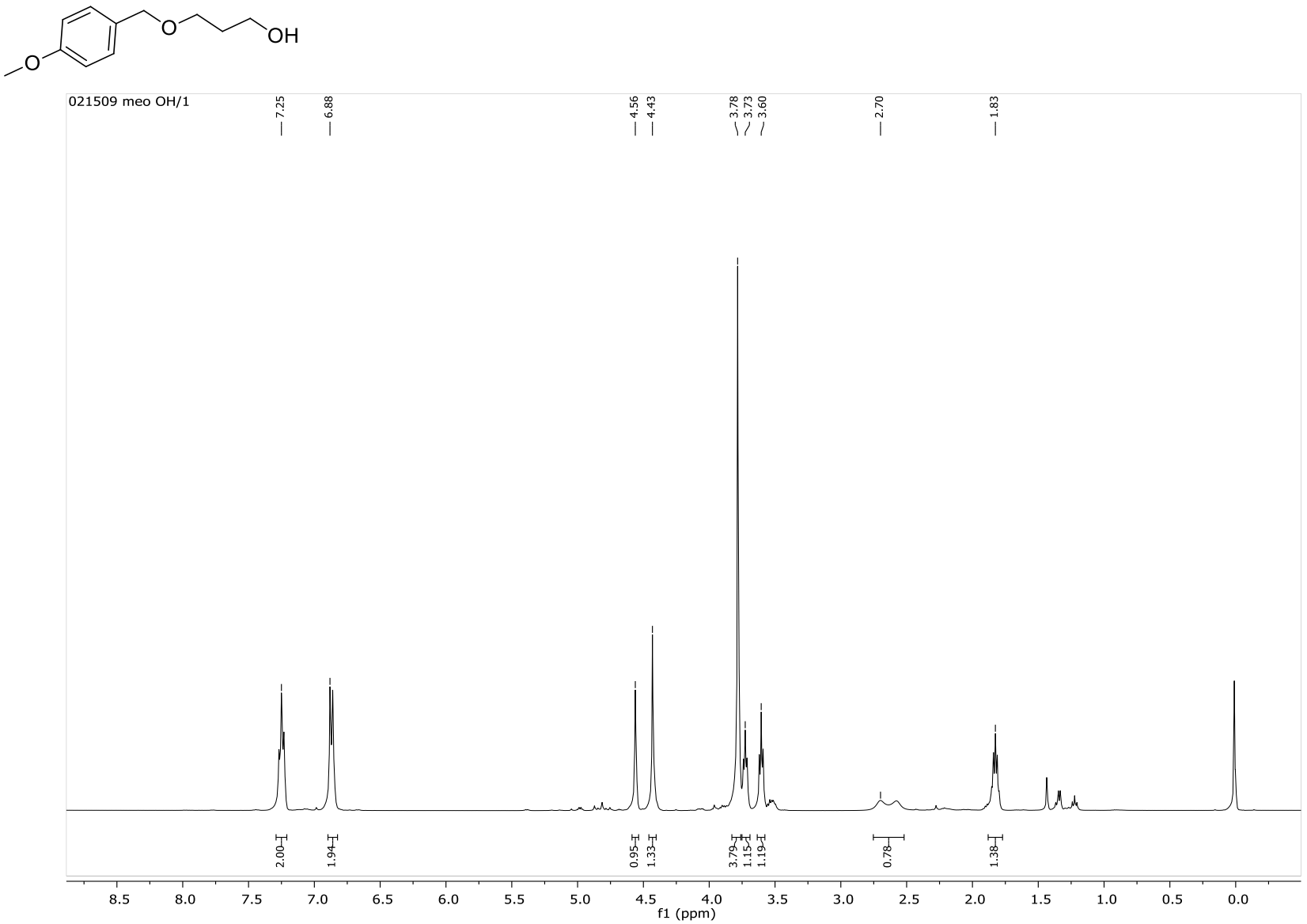
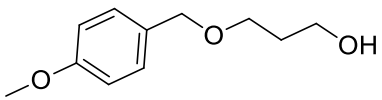


Figure 27. 3-(4-Methoxybenzyloxy)propan-1-ol, ^{1}H-NMR (400MHz, $CDCl_3$)



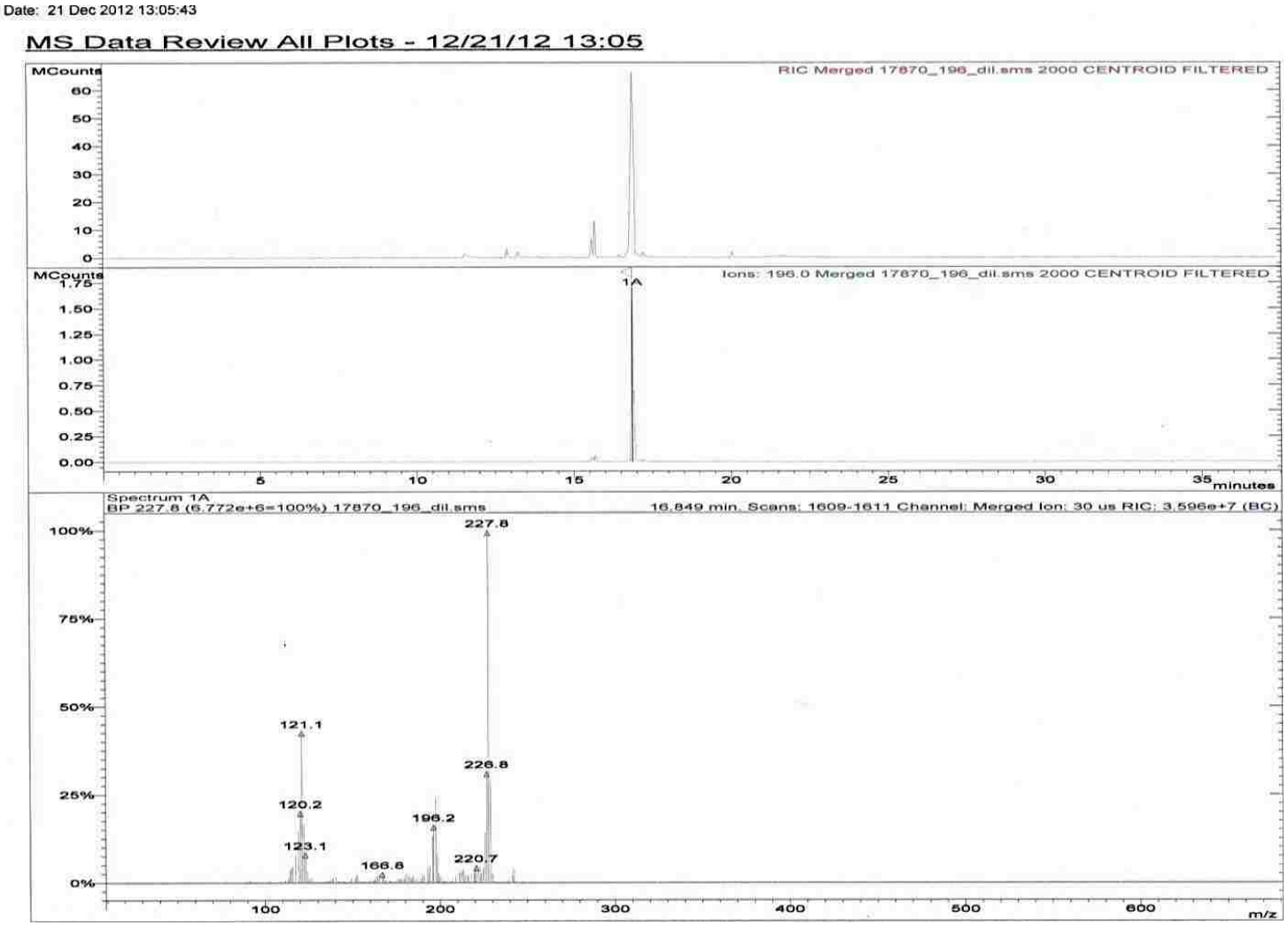
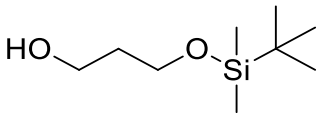


Figure 28. 3-(4-Methoxybenzyloxy)propan-1-ol, GC/MS EI (filament voltage 70 eV)



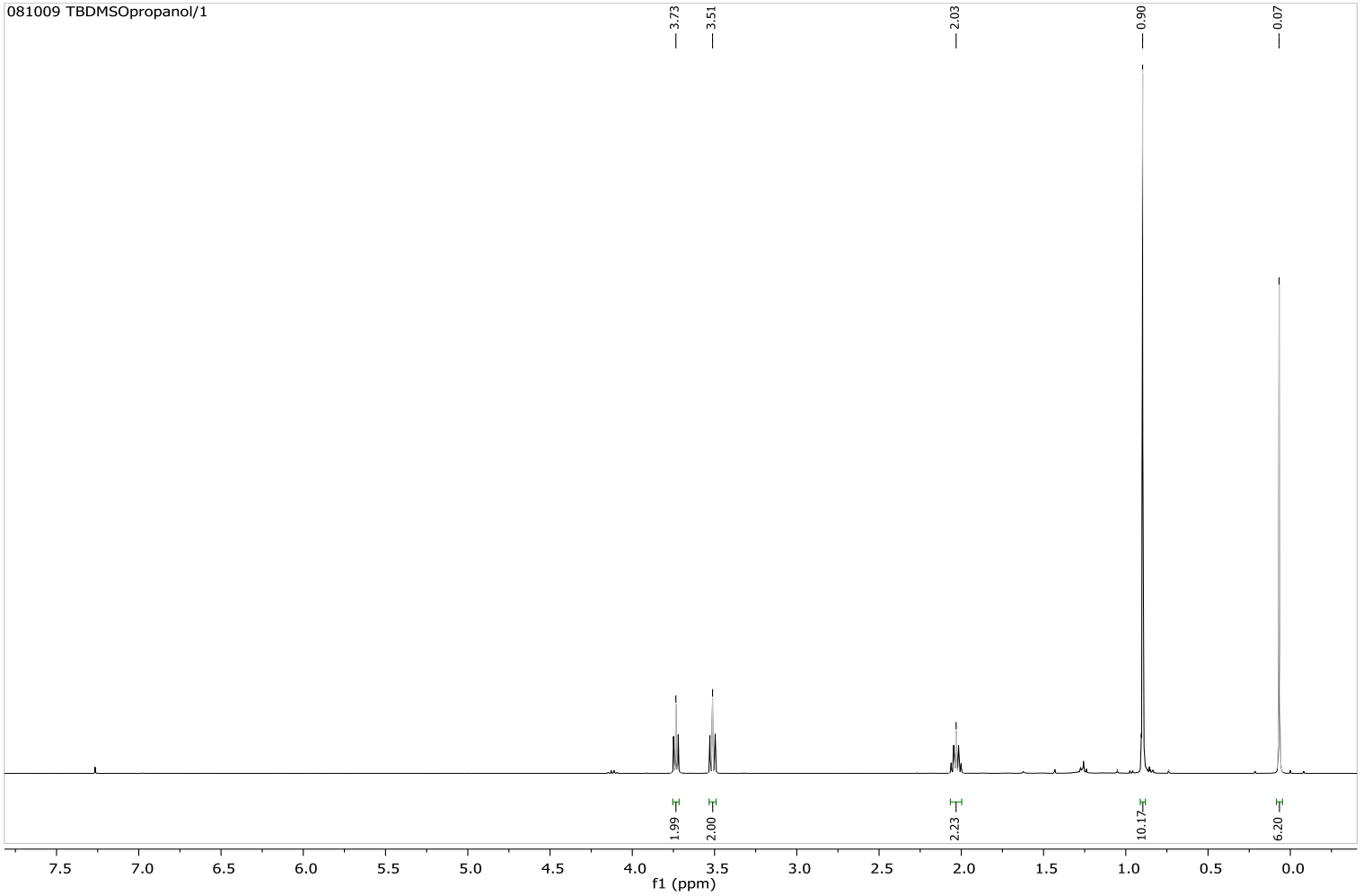
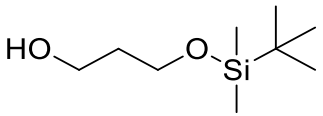


Figure 29. 3-((tert-butyldimethylsilyl)oxy)propan-1-ol, ^{1}H-NMR (400MHz, $CDCl_3$)



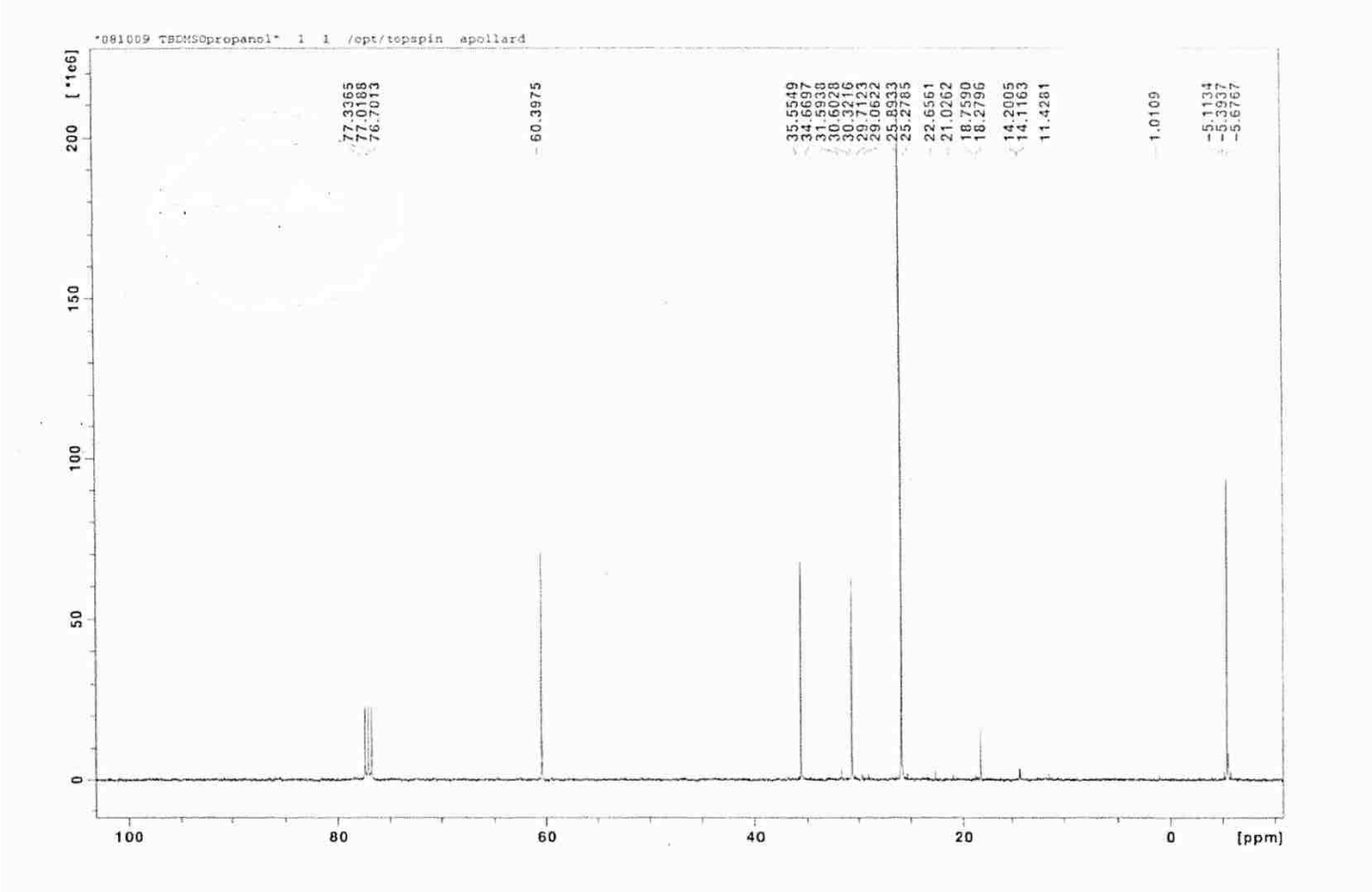


Figure 30. 3-((tert-butyldimethylsilyl)oxy)propan-1-ol, ^{13}C-NMR (101MHz, $CDCl_3$)

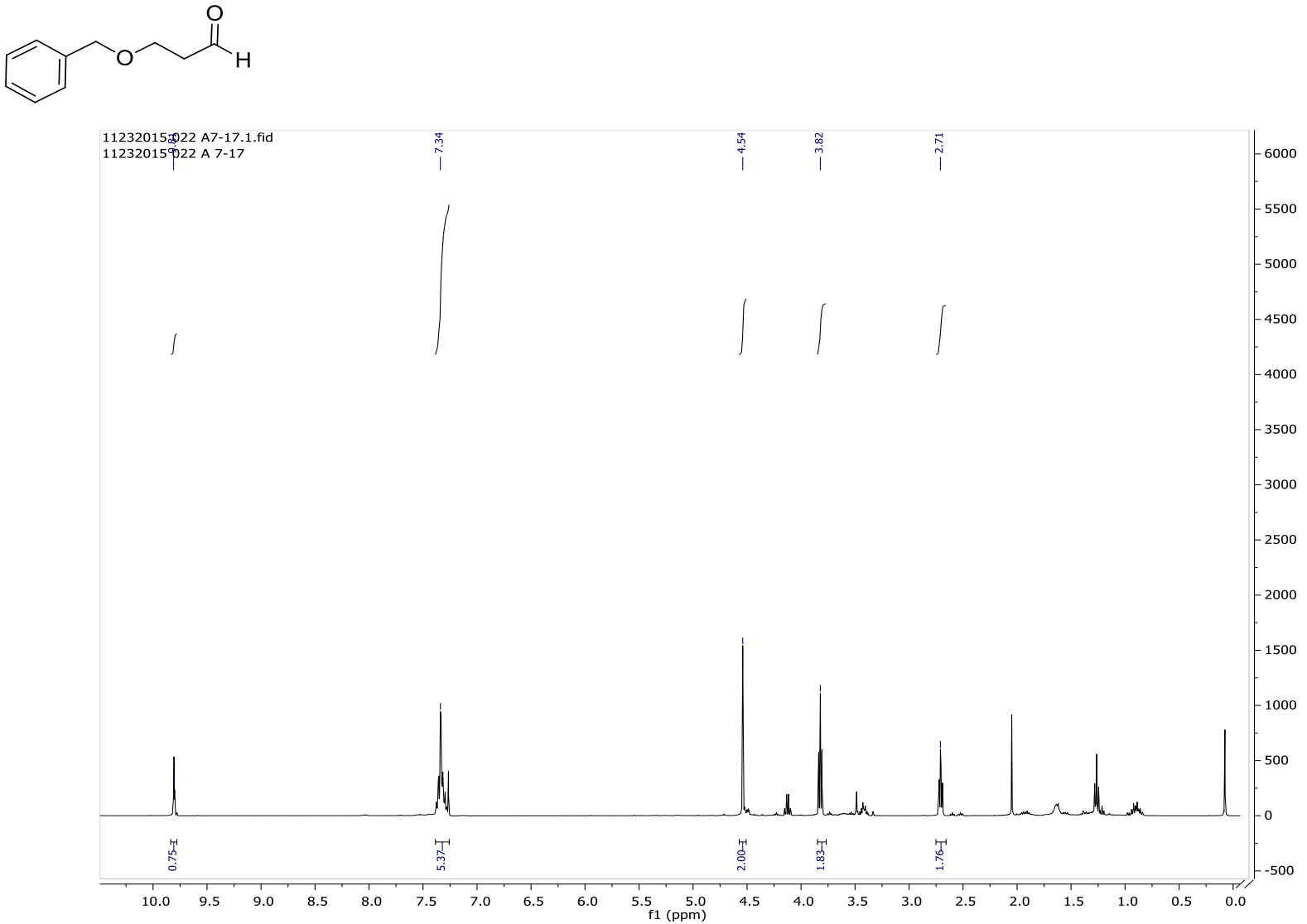
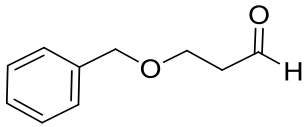


Figure 31. (3-Benzyloxy)propanal,^{1}H-NMR (400MHz, $CDCl_3$)



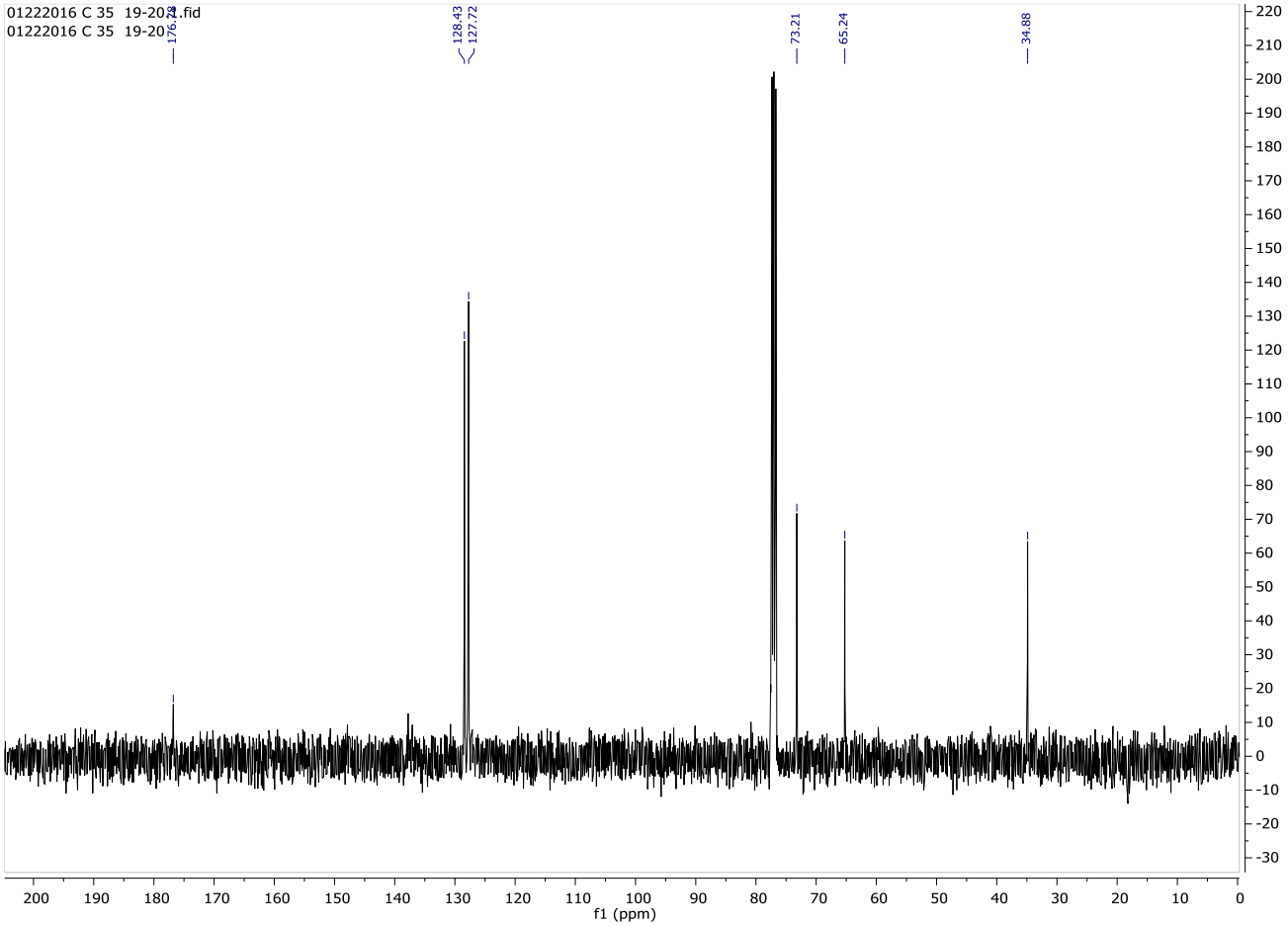
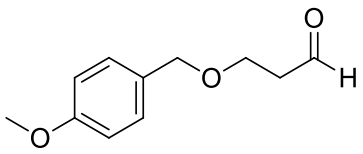


Figure 32. (3-Benzyloxy)propanal, ^{13}C-NMR (101MHz, $CDCl_3$)



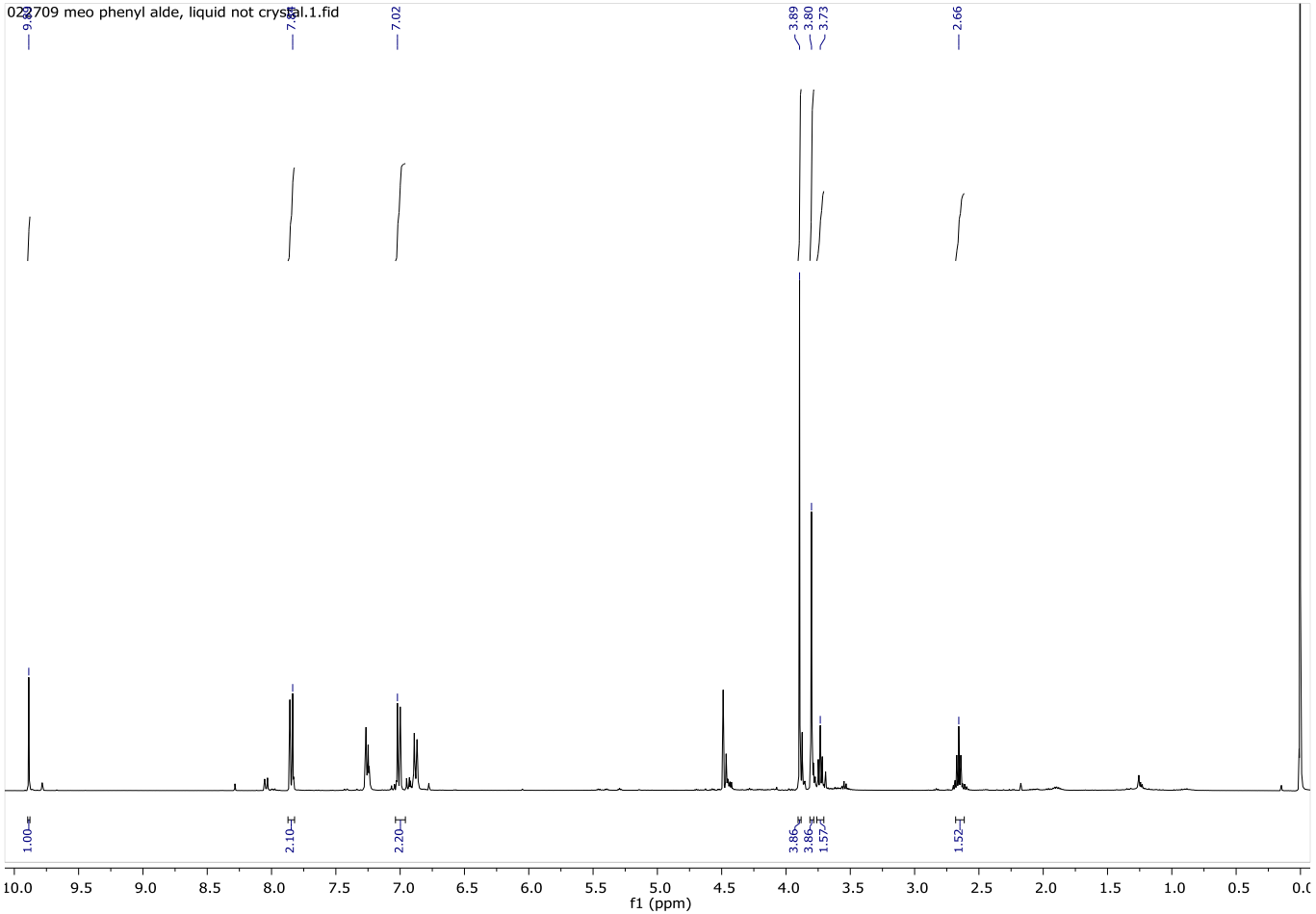
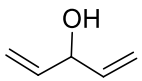


Figure 33. 3-(4-Methoxybenzyloxy)propanal, ^{1}H-NMR (400MHz, $CDCl_3$)



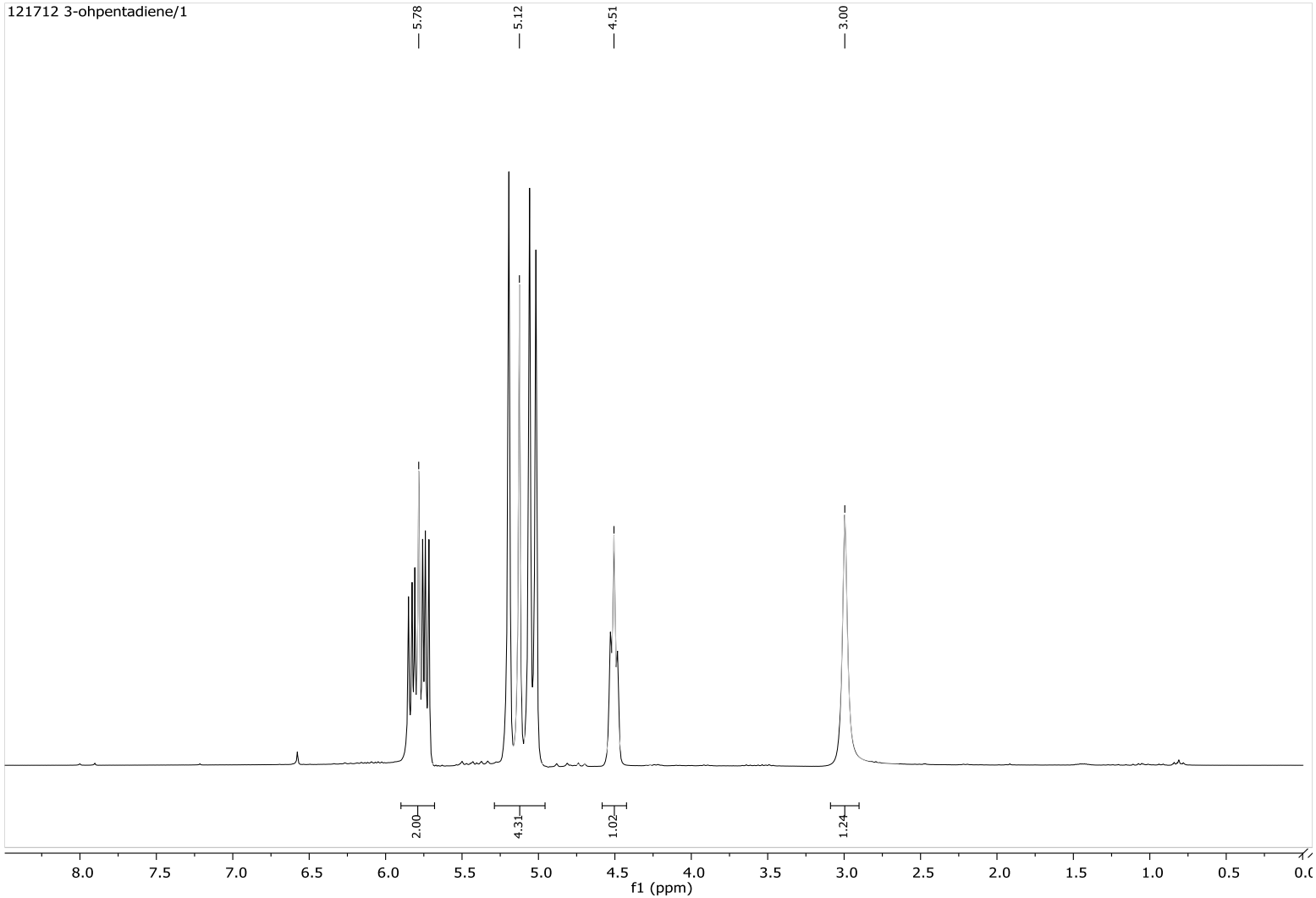
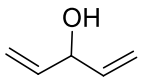


Figure 34. Penta-1,4-dien-3-ol, ^{1}H-NMR (400MHz, $CDCl_3$)



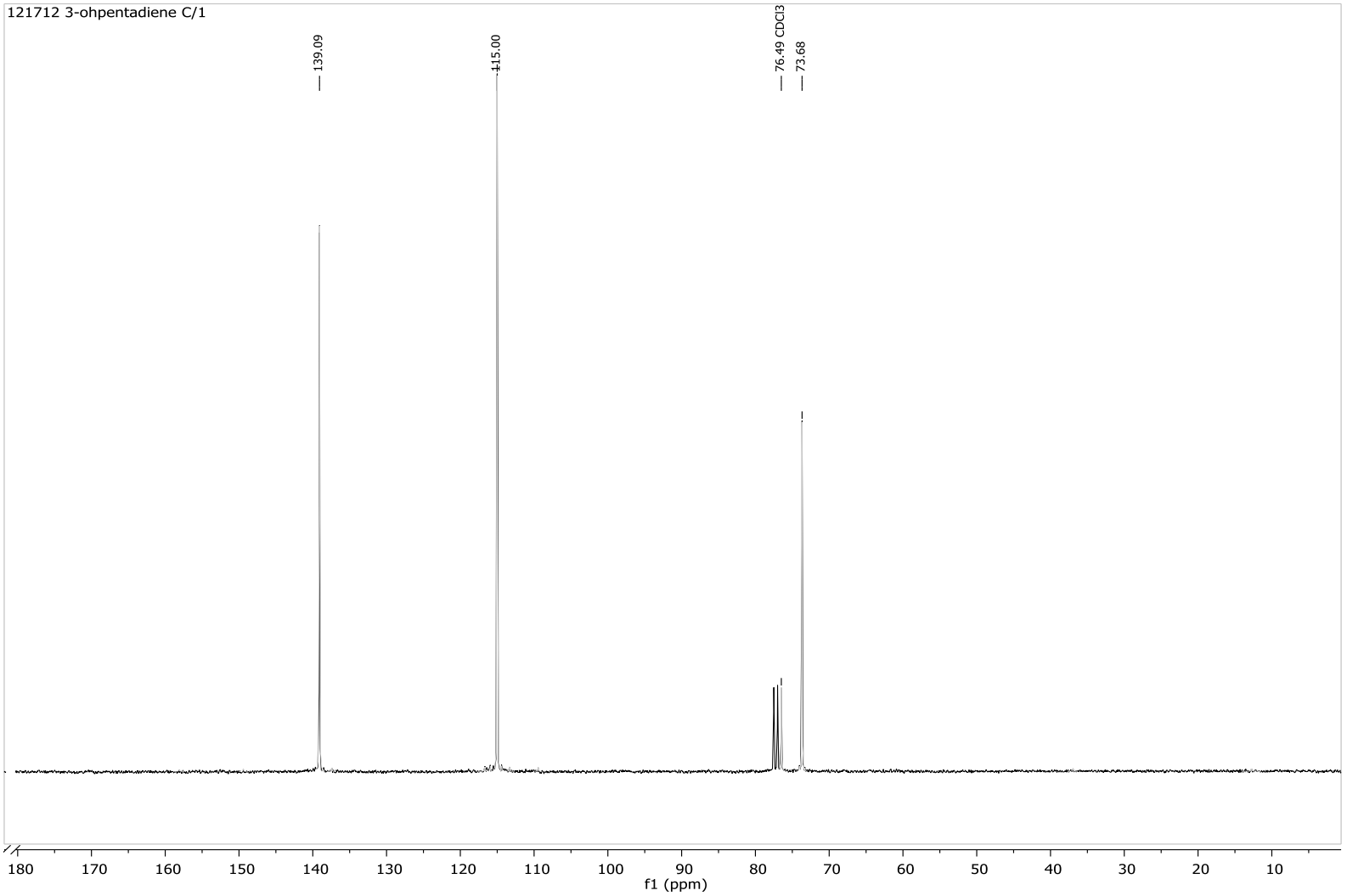


Figure 35. Penta-1,4-dien-3-ol, ^{13}C-NMR (101MHz, $CDCl_3$)

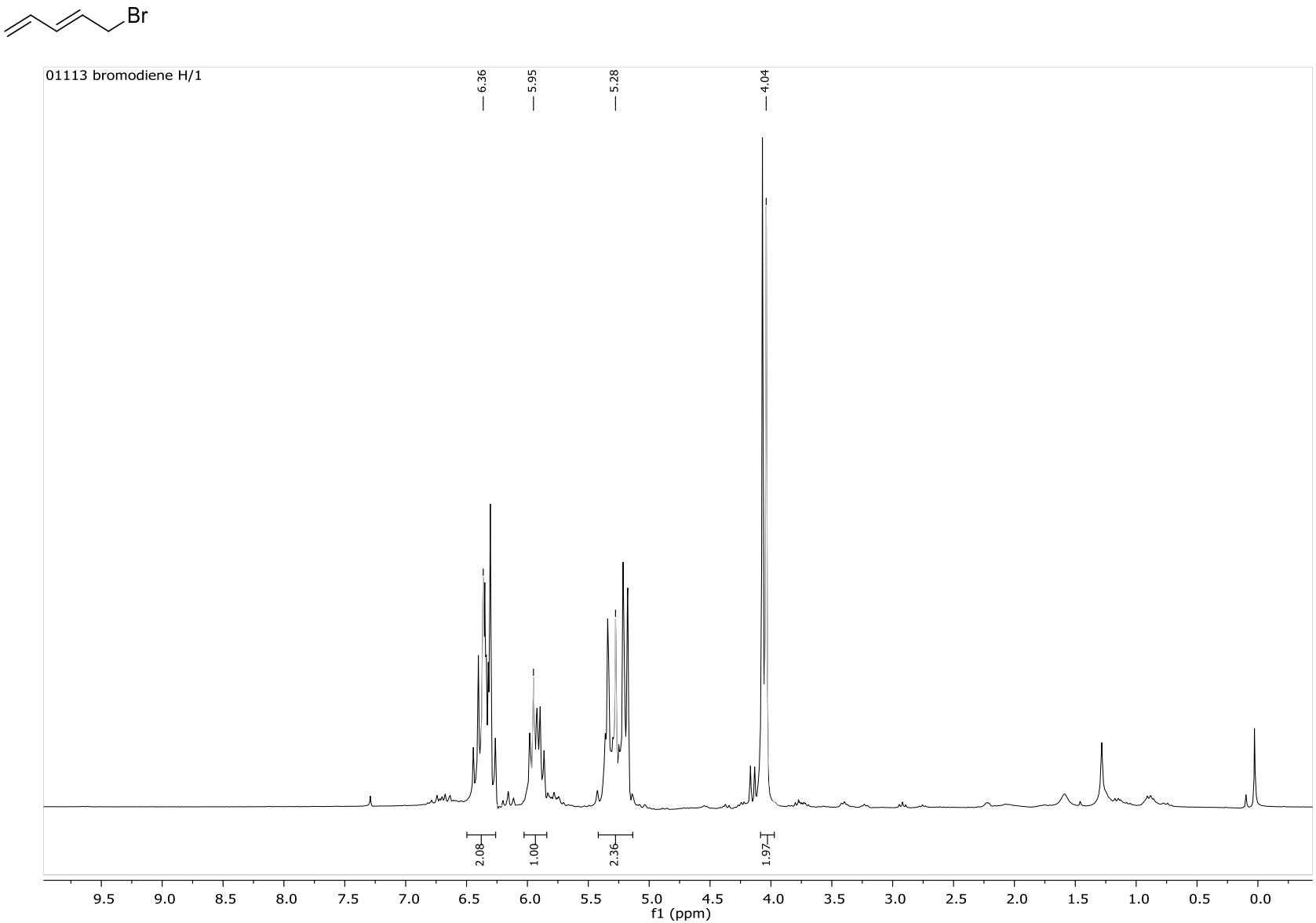


Figure 36. (E)-5-Bromopenta-1,3-diene, ^{1}H-NMR (400MHz, $CDCl_3$)

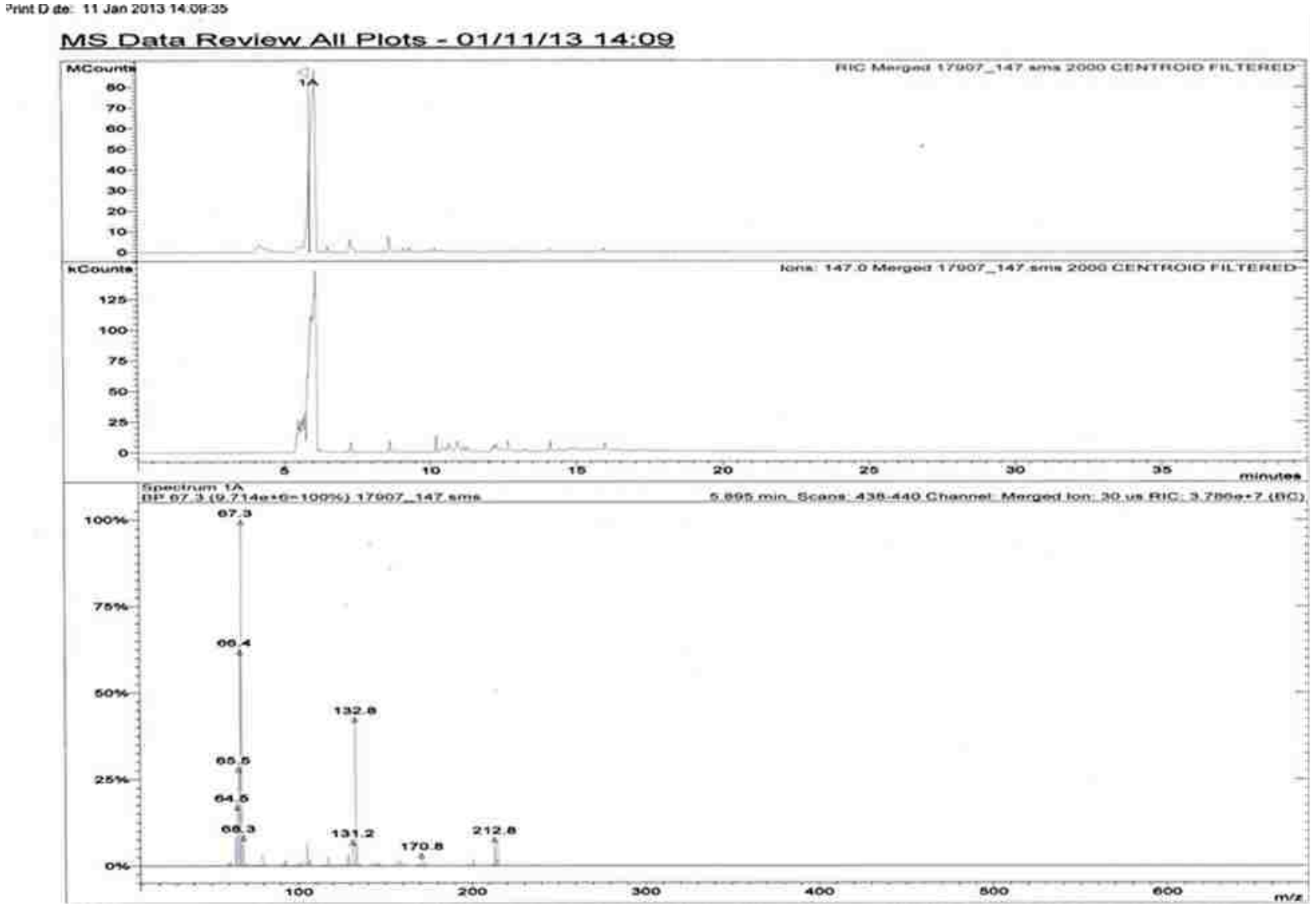
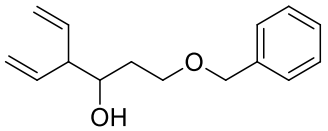


Figure 37. (E)-5-Bromopenta-1,3-diene, GC/MS EI (filament voltage 70 eV)



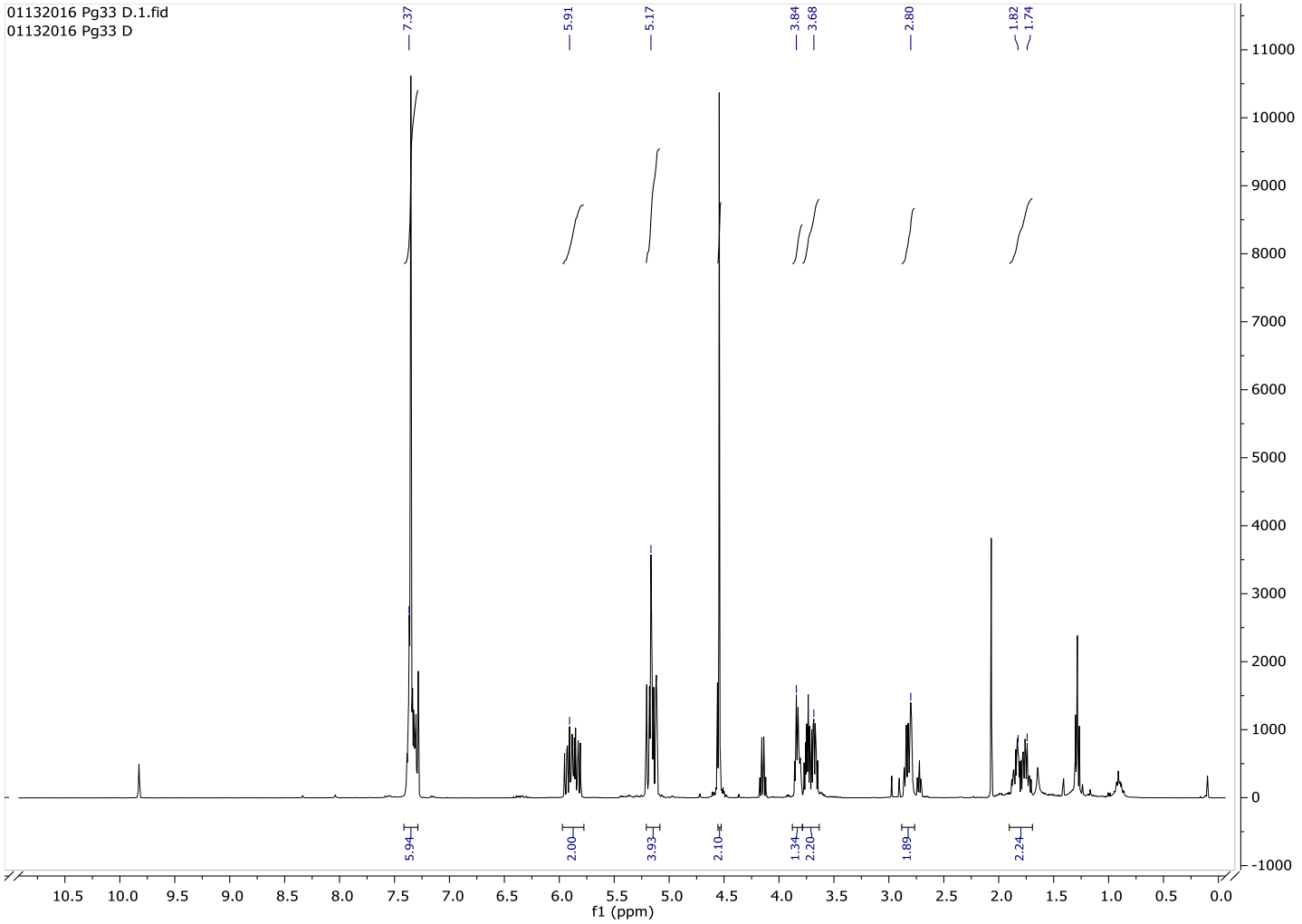
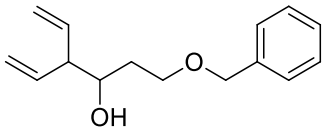


Figure 38. 1-(Benzyloxy)-4-vinylhex-5-en-3-ol,^{1}H-NMR (400MHz, $CDCl_3$)



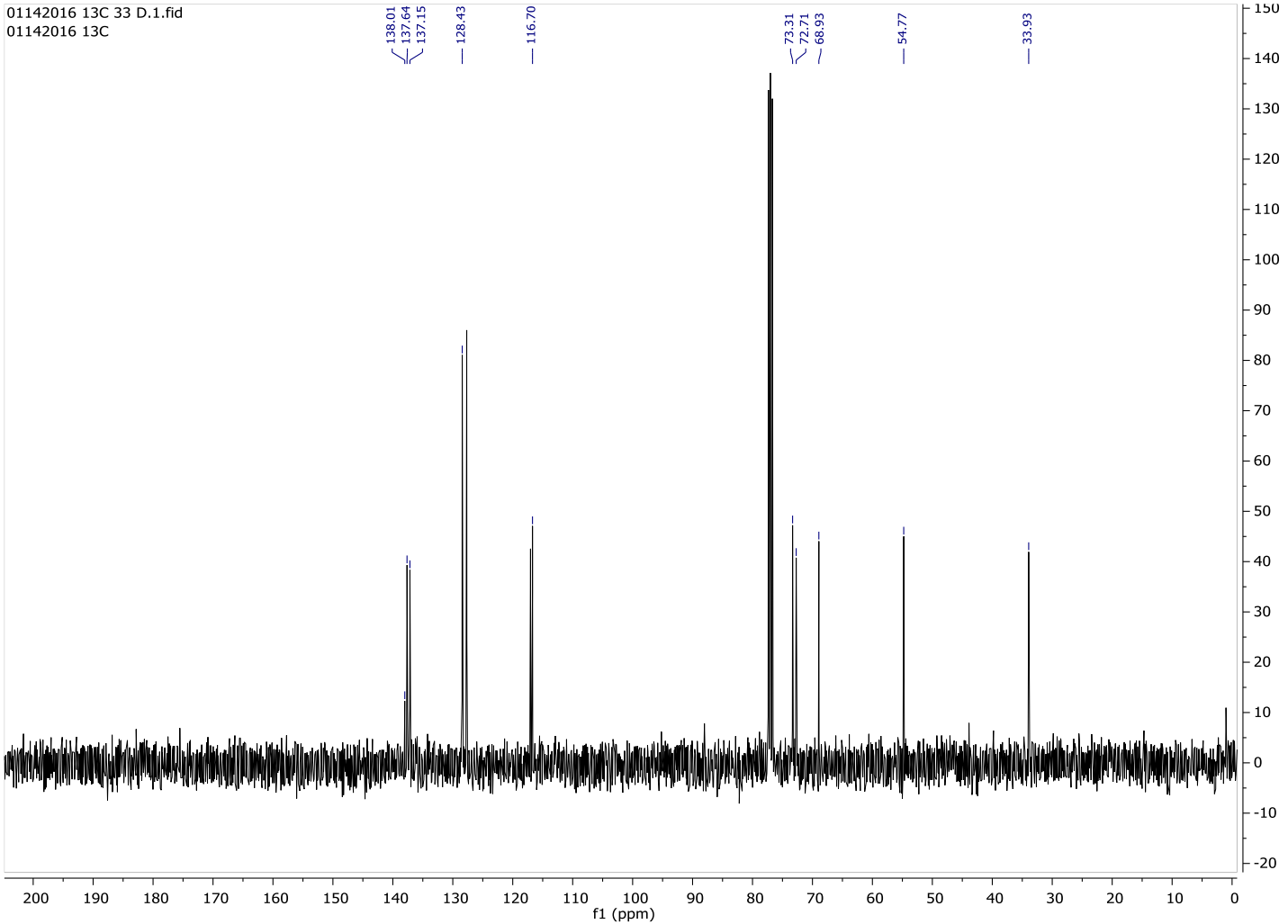


Figure 39. 1-(Benzyloxy)-4-vinylhex-5-en-3-ol ^{13}C-NMR (101MHz, $CDCl_3$)

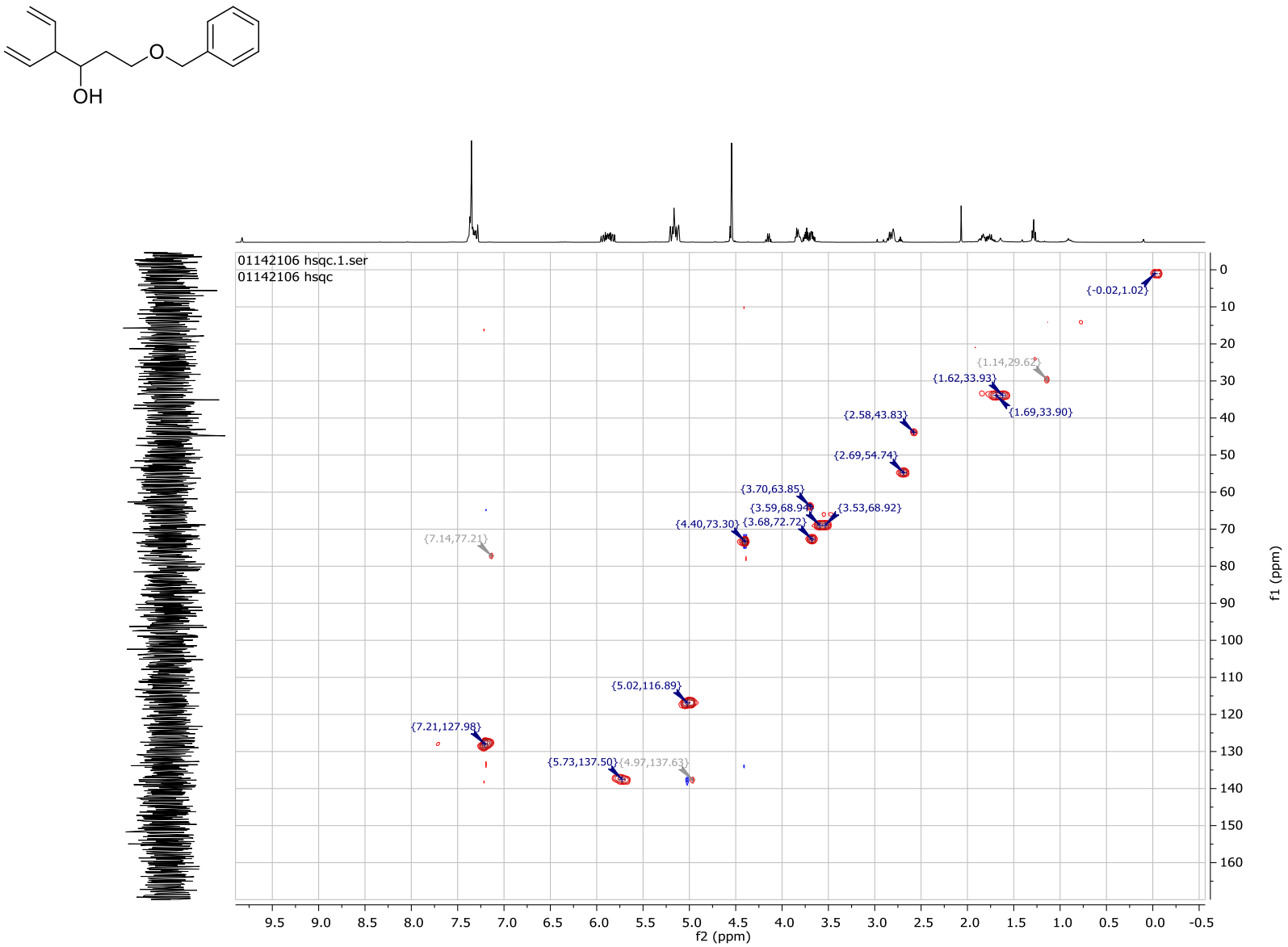


Figure 40. 1-(Benzyloxy)-4-vinylhex-5-en-3-ol, HSQC

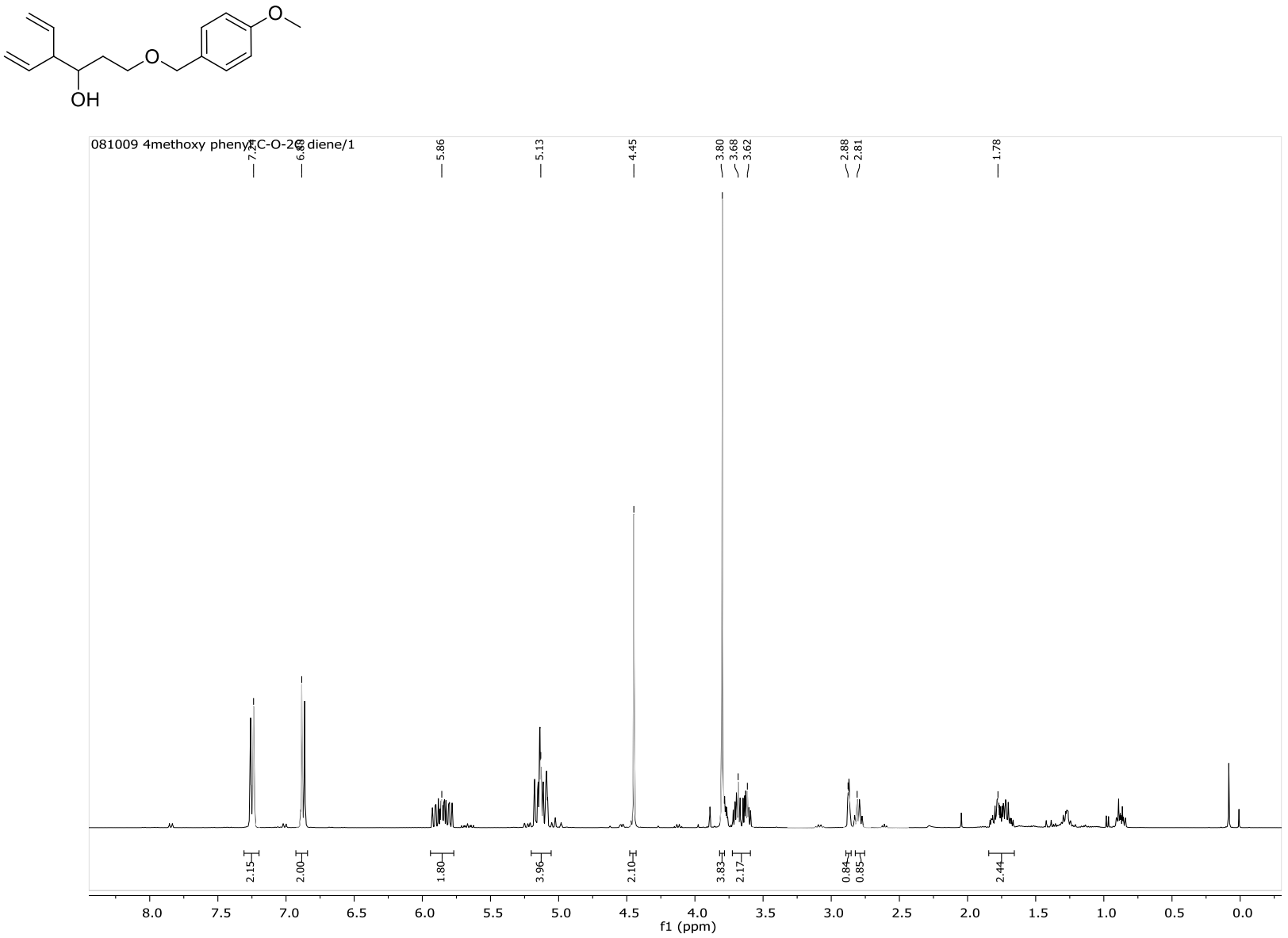
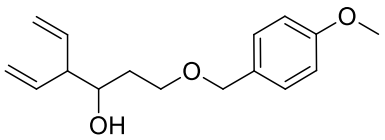


Figure 41. 1-(4-Methoxybenzyloxy)-4-vinylhex-5-en-3-ol, ^{1}H-NMR (400MHz, $CDCl_3$)



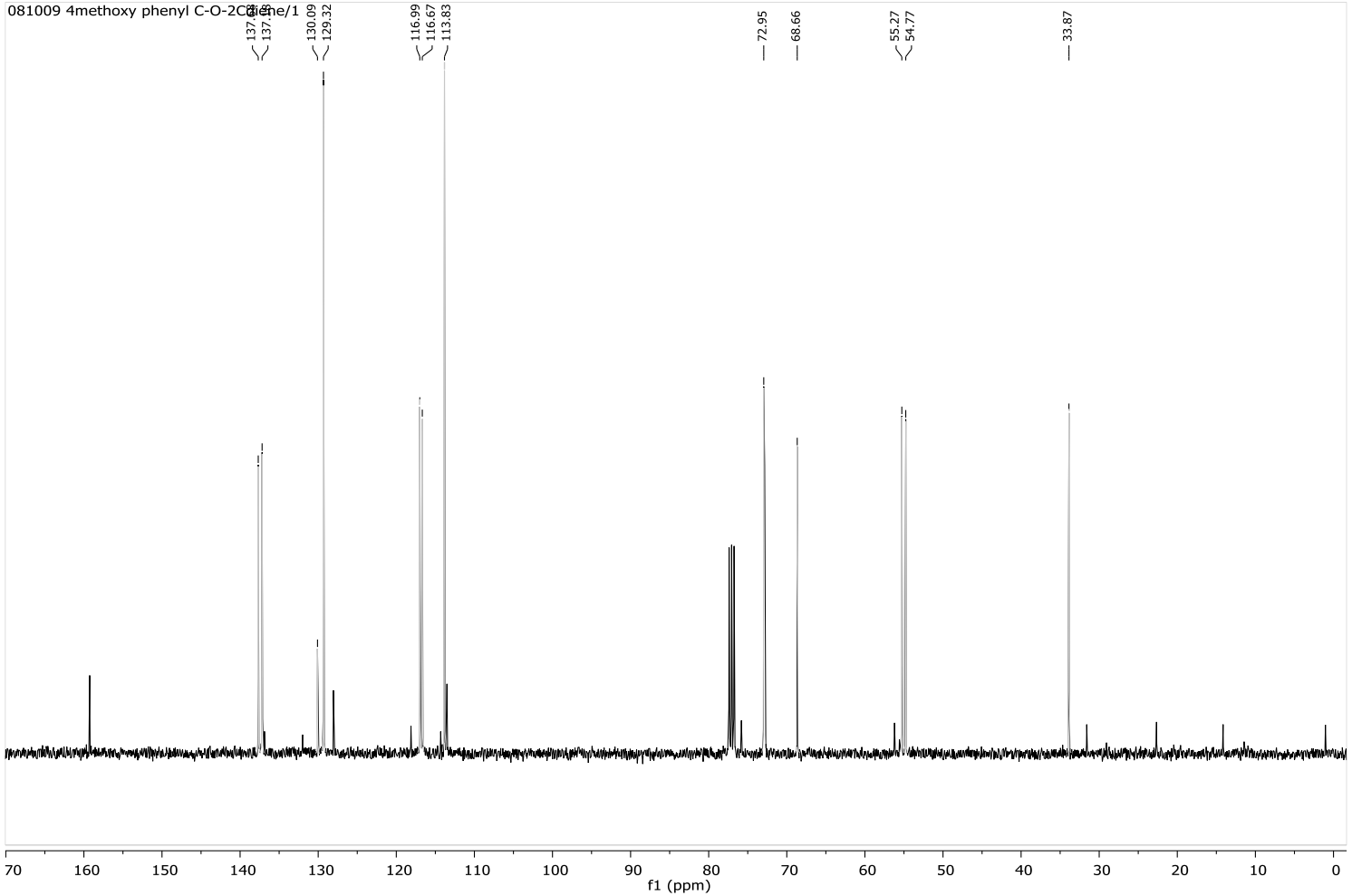
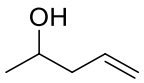


Figure 42. 1-(4-Methoxybenzyloxy)-4-vinylhex-5-en-3-ol, ^{13}C-NMR (101MHz, $CDCl_3$)



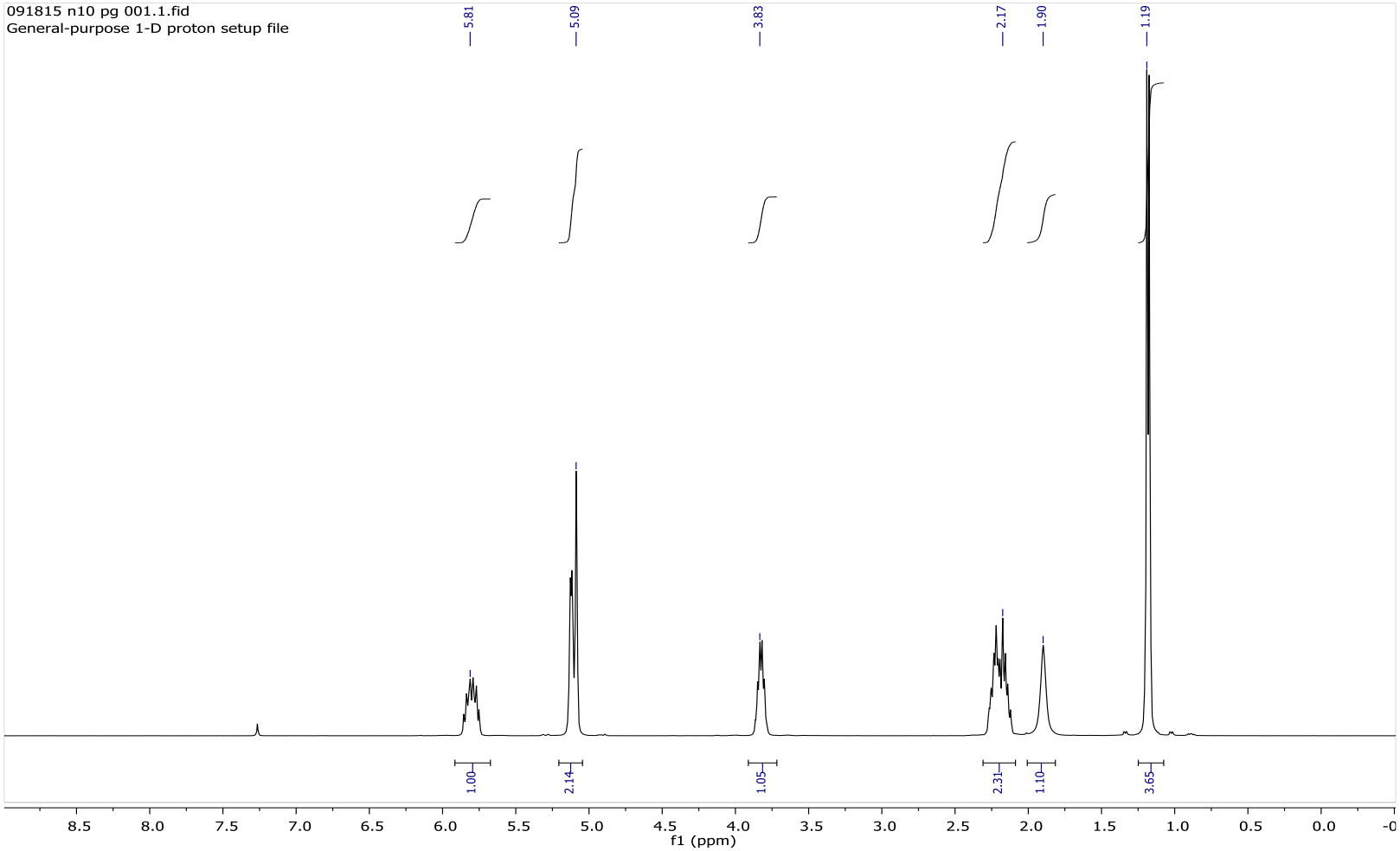
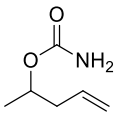


Figure 43. 4-penten-2-ol, ^{1}H-NMR (400 MHz, $CDCl_3$)



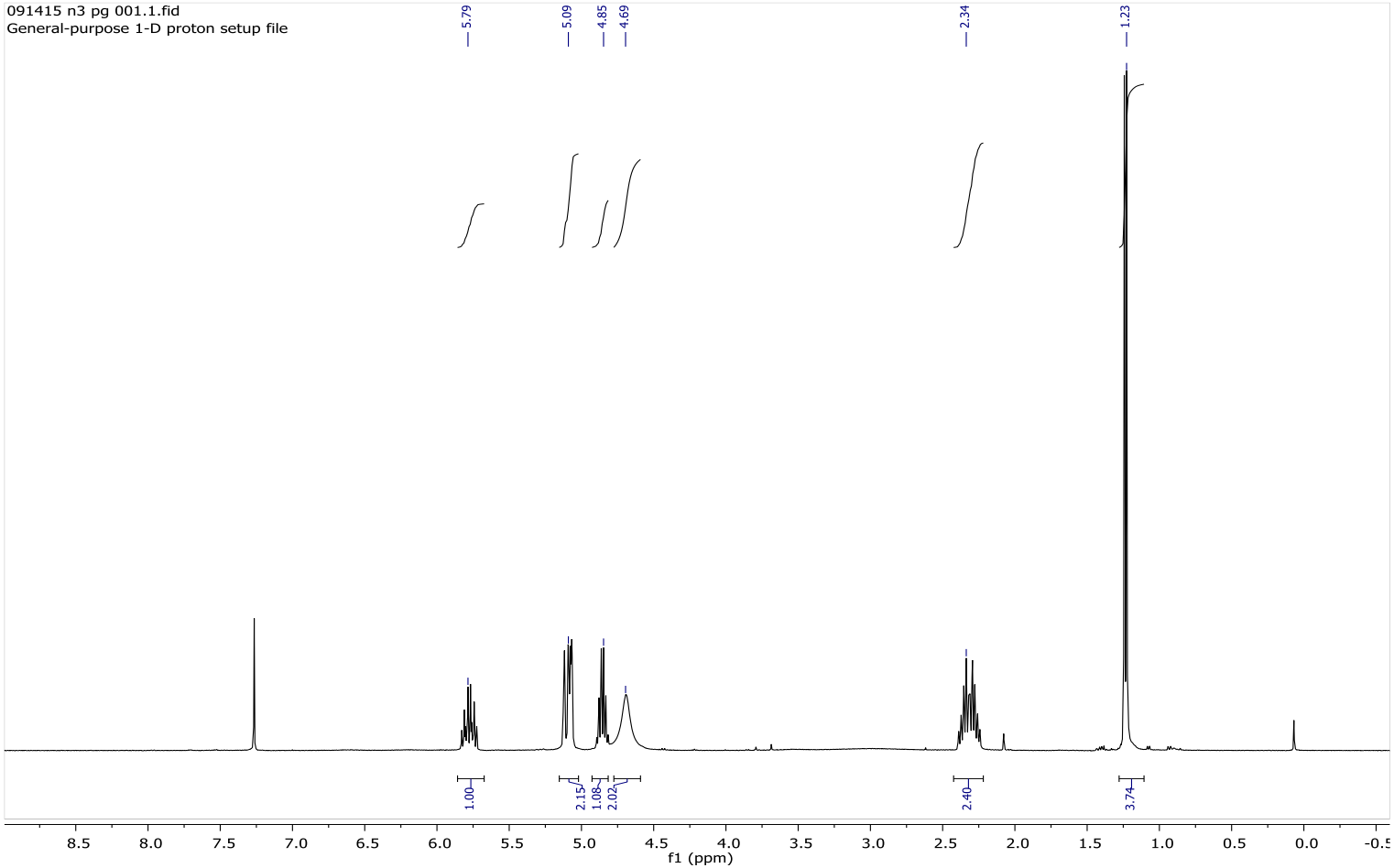
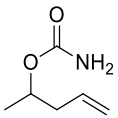


Figure 44. Pent-4-en-2-yl carbamate, ^{1}H-NMR (400 MHz, $CDCl_3$)



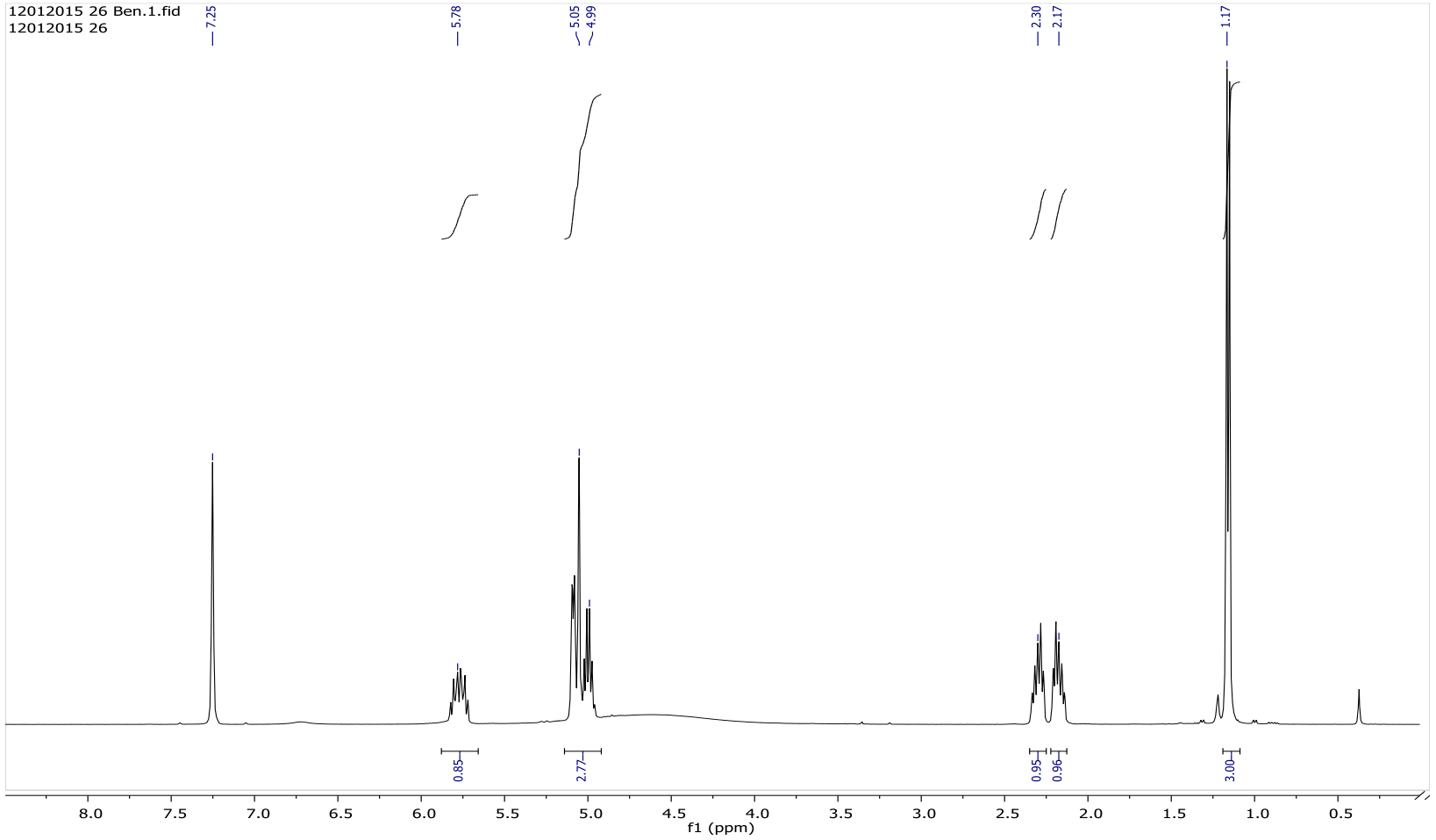
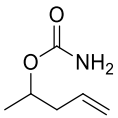


Figure 45 Pent-4-en-2-yl carbamate, ^{1}H-NMR (400 MHz, C_6D_6)



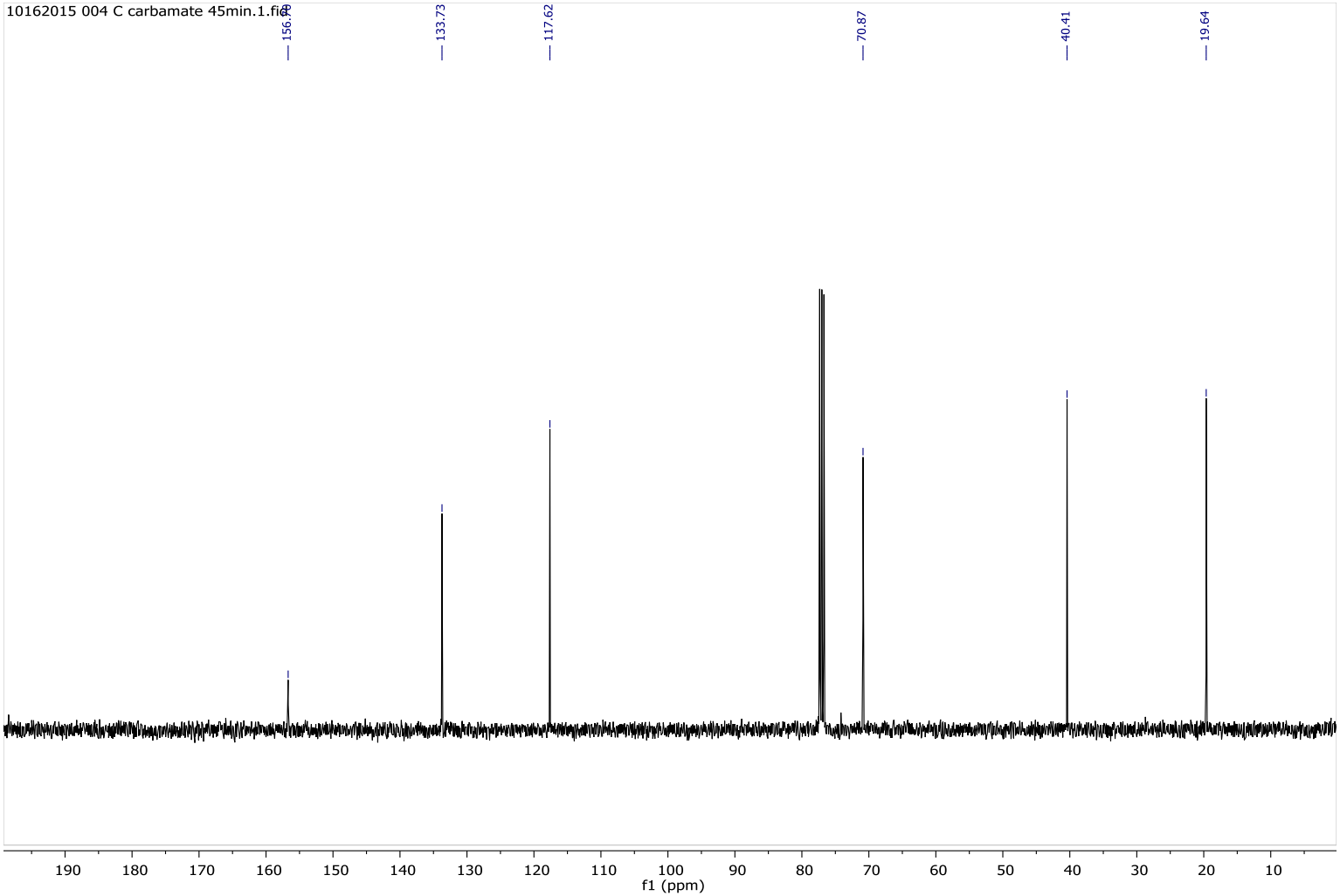


Figure 46. Pent-4-en-2-yl carbamate, ^{13} C-NMR (101 MHz, $CDCl_3$)

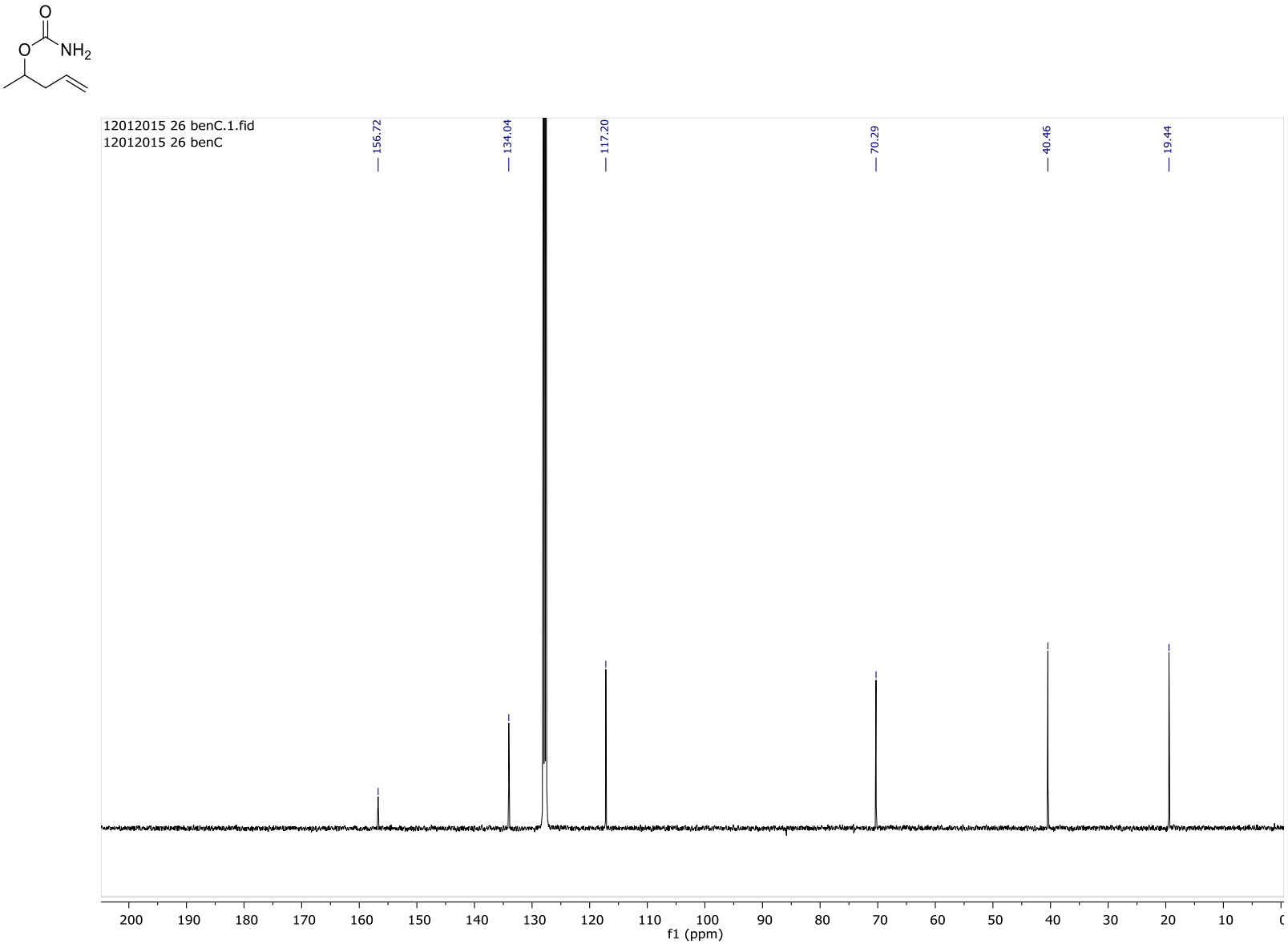
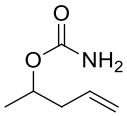


Figure 47. Pent-4-en-2-yl carbamate, ^{13} C-NMR (101 MHz, C_6D_6)



m/z: 129

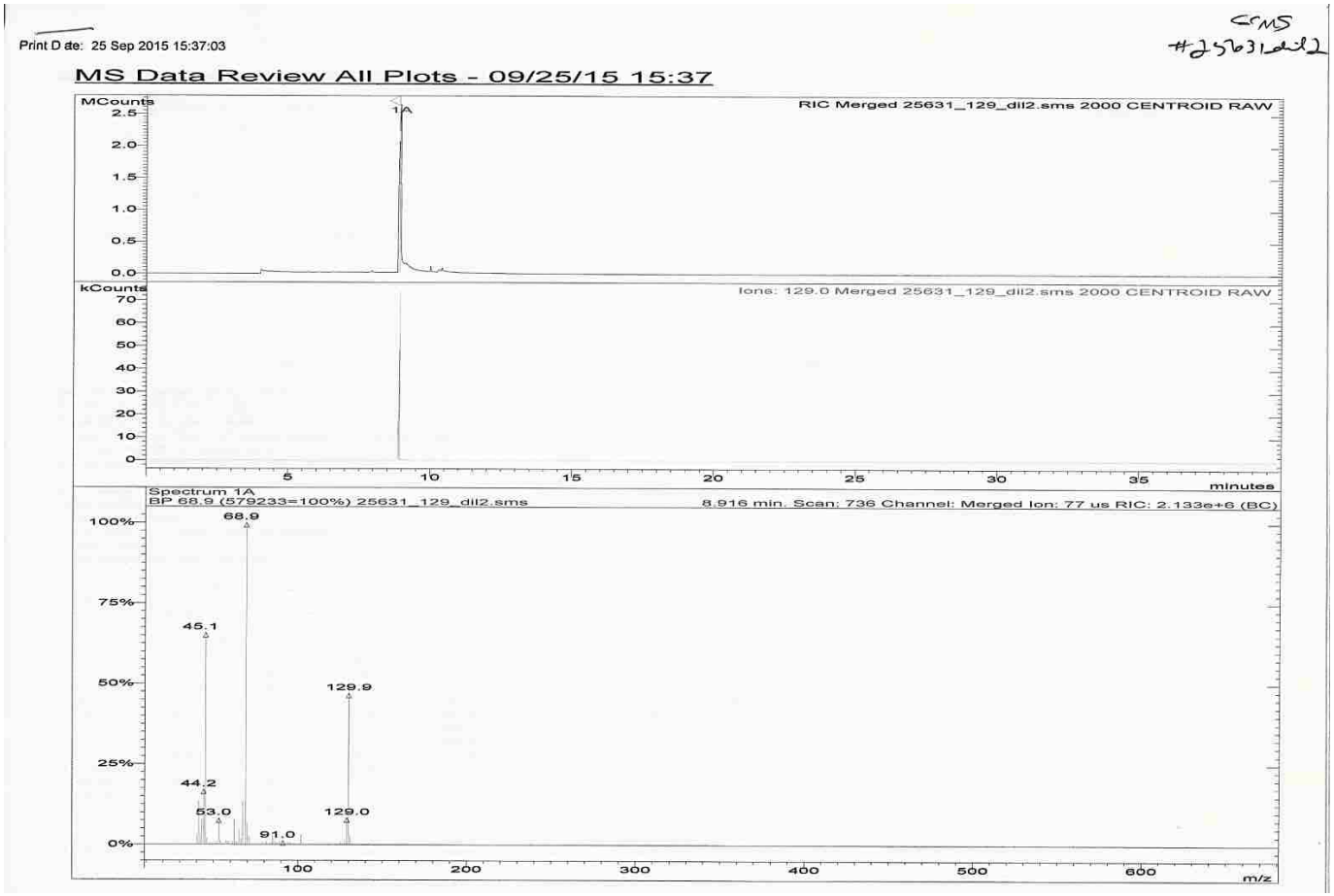
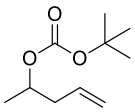


Figure 48. GC/MS of pent-4-en-2-yl carbamate, EI (filament voltage 70 eV)



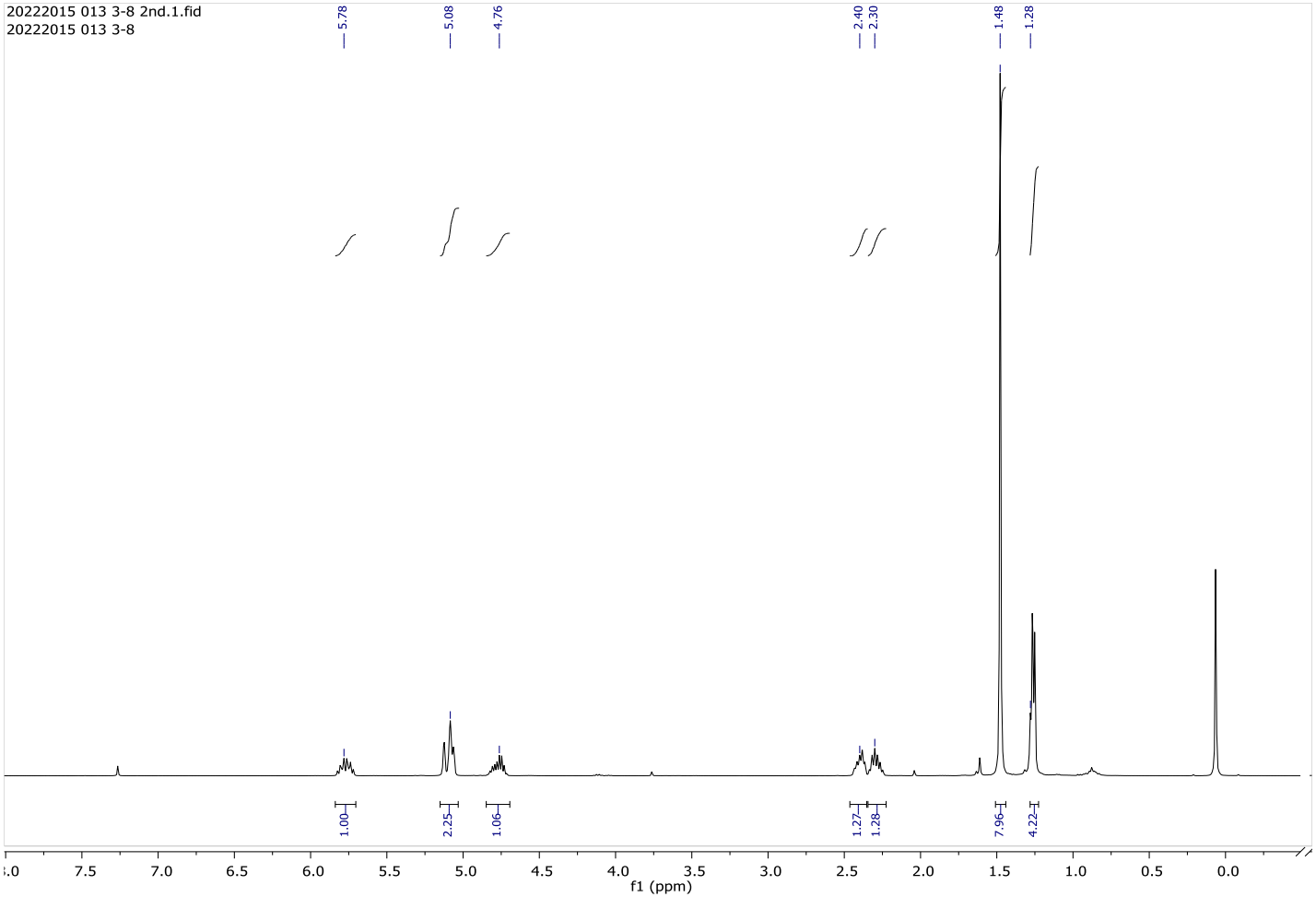
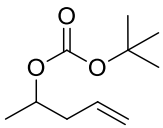


Figure 49. Tert-butyl pent-4-en-2-yl carbonate product from Kumar, D.N., 2011 procedure purified using $AgNO_3$ 10 wt% on silica, ^{1}H-NMR (400 MHz, $CDCl_3$)



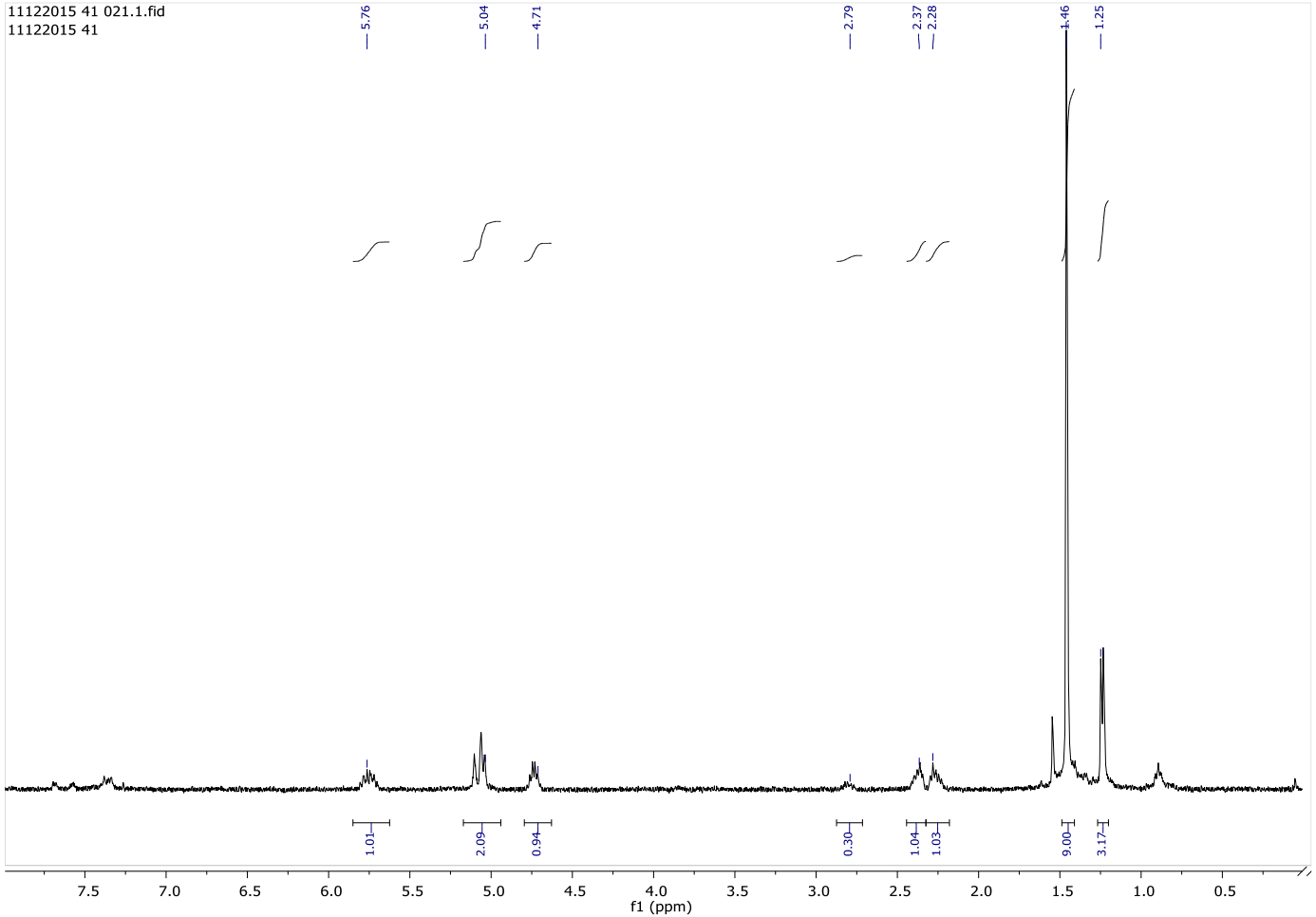
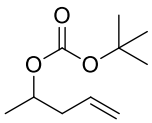


Figure 50. Tert-butyl pent-4-en-2-yl carbonate reaction crude using Duan, J. J. W.; Smith, A. B. procedure. ^{1}H NMR (400 MHz, $CDCl_3$)



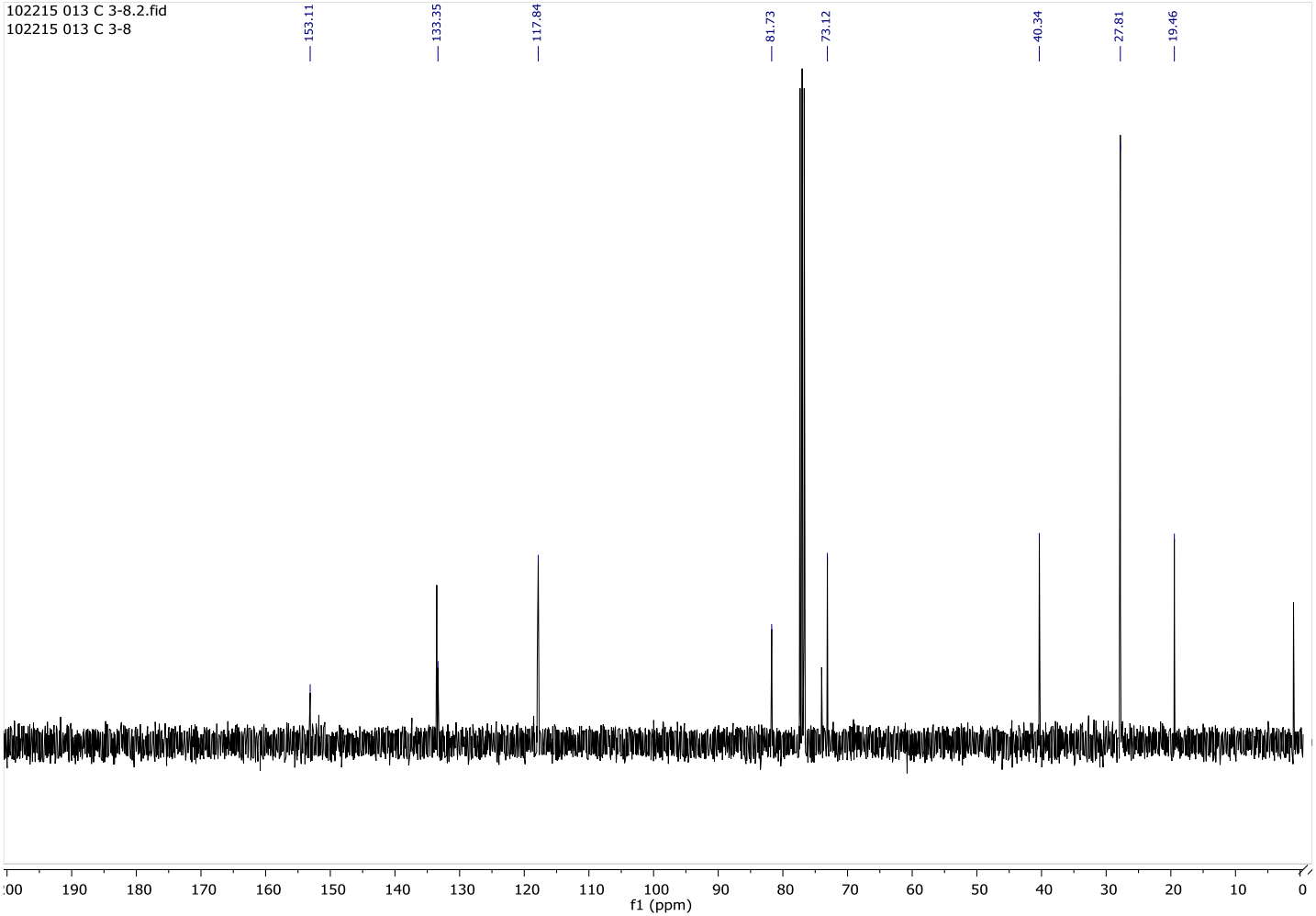
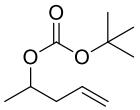


Figure 51. Tert-butyl pent-4-en-2-yl carbonate product from Kumar, D.N., 2011 procedure purified using $AgNO_3$ 10 wt% on silica, ^{13}C-NMR (101 MHz, $CDCl_3$)



m/z: 186

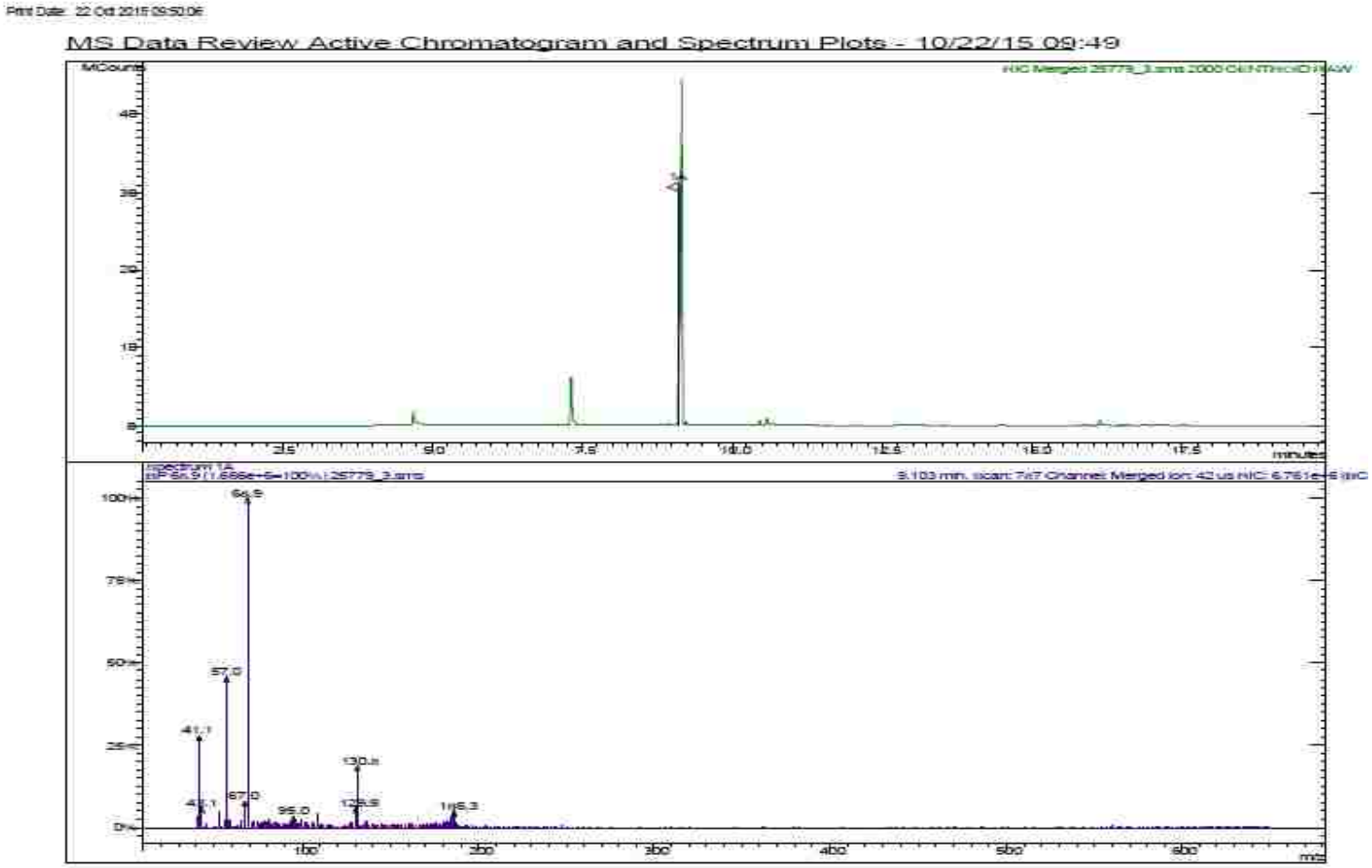
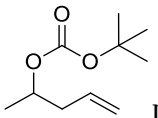


Figure 52. GC/MS chromatograph and spectra of tert-butyl pent-4-en-2-yl carbonate product from Kumar, D.N., 2011 procedure purified using $AgNO_3$ 10 wt% on silica, EI (filament voltage 70 eV)



m/z 186

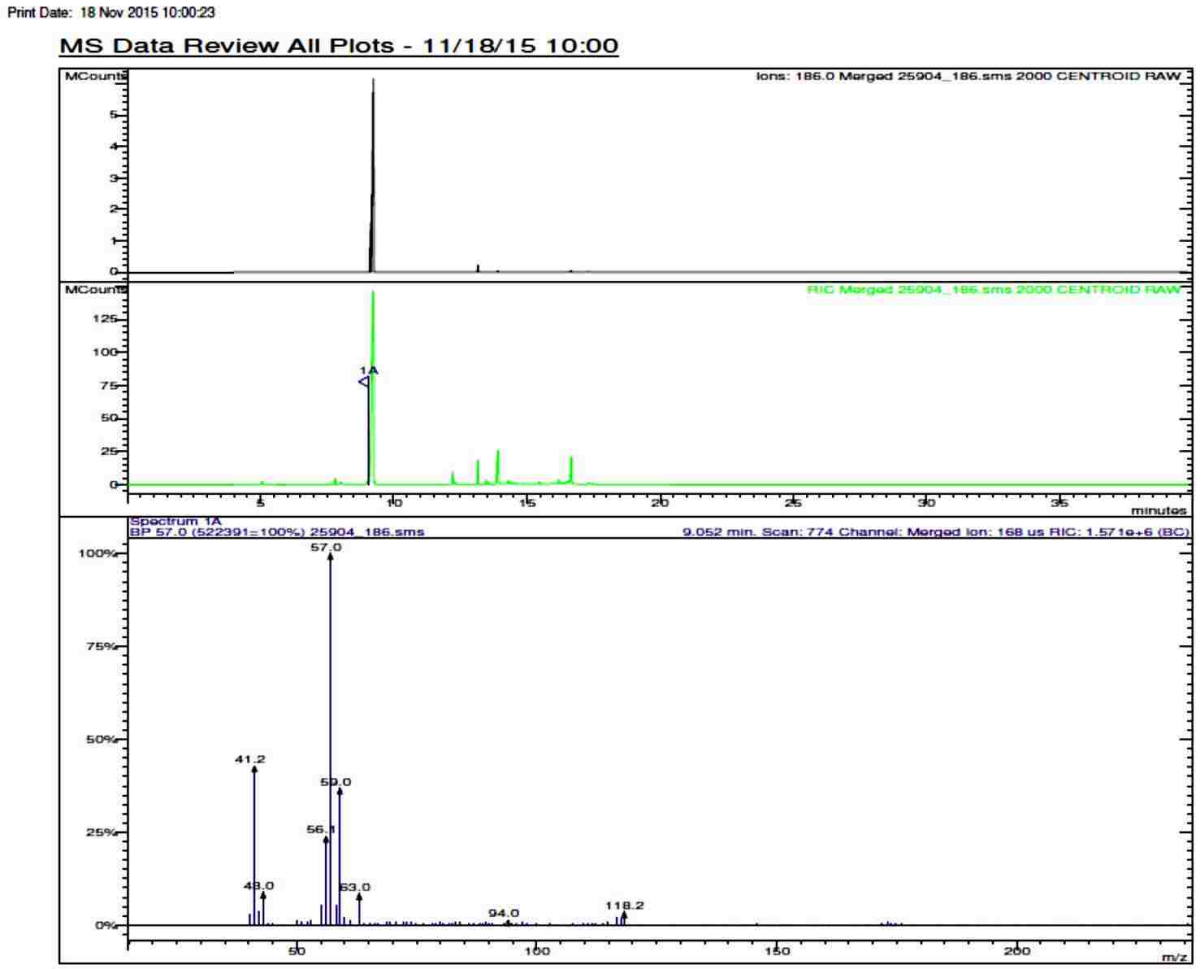
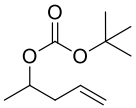


Figure 53. GC/MS chromatograph and spectra of tert-butyl pent-4-en-2-yl carbonate reaction crude Duan, J. J. W.; Smith, A. B. procedure, EI (filament voltage 70 eV)



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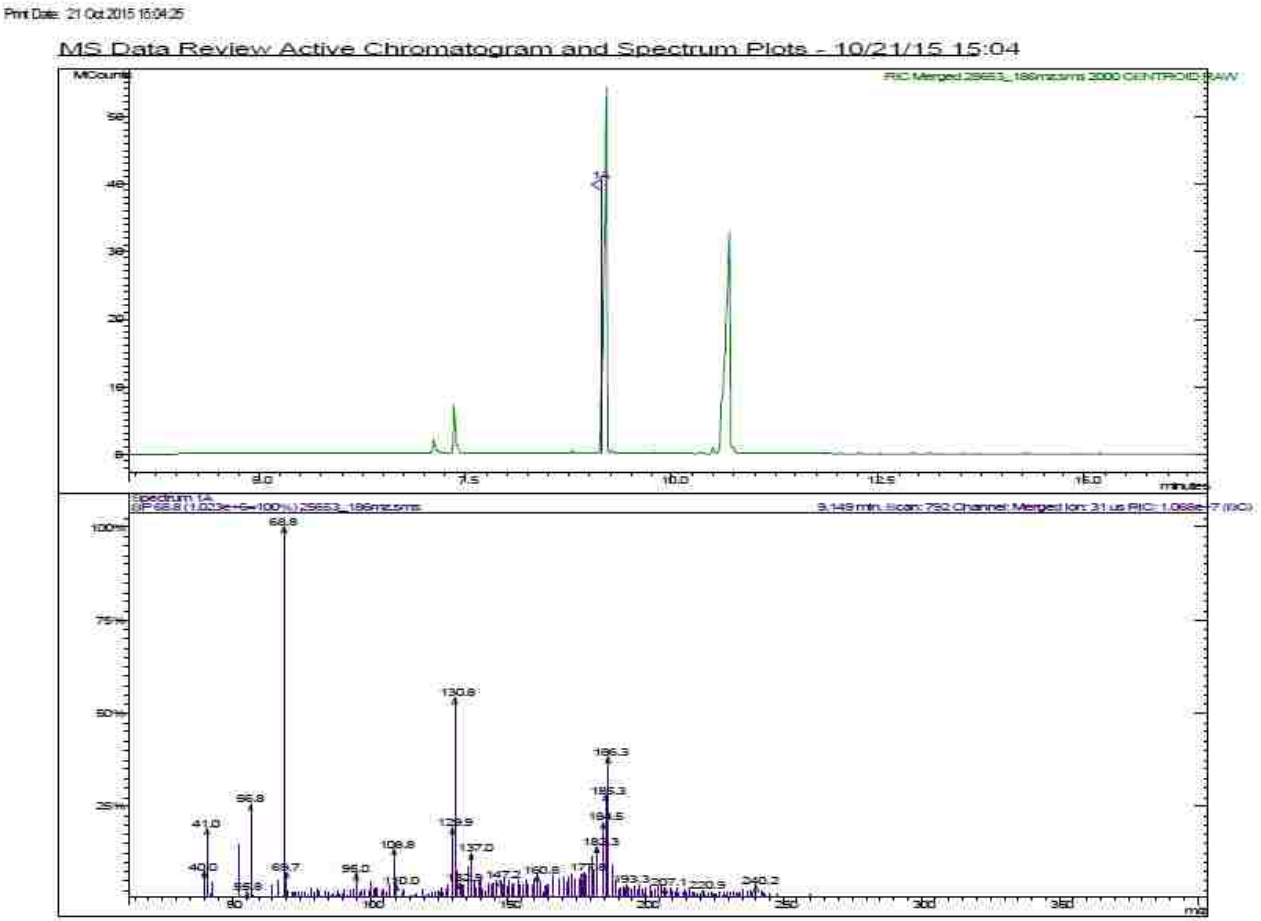
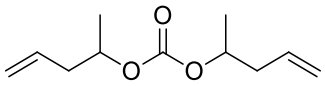


Figure 54. GC/MS chromatograph and spectra of tert-butyl pent-4-en-2-yl carbonate reaction mixture, EI (filament voltage 70 eV)



m/z: 198

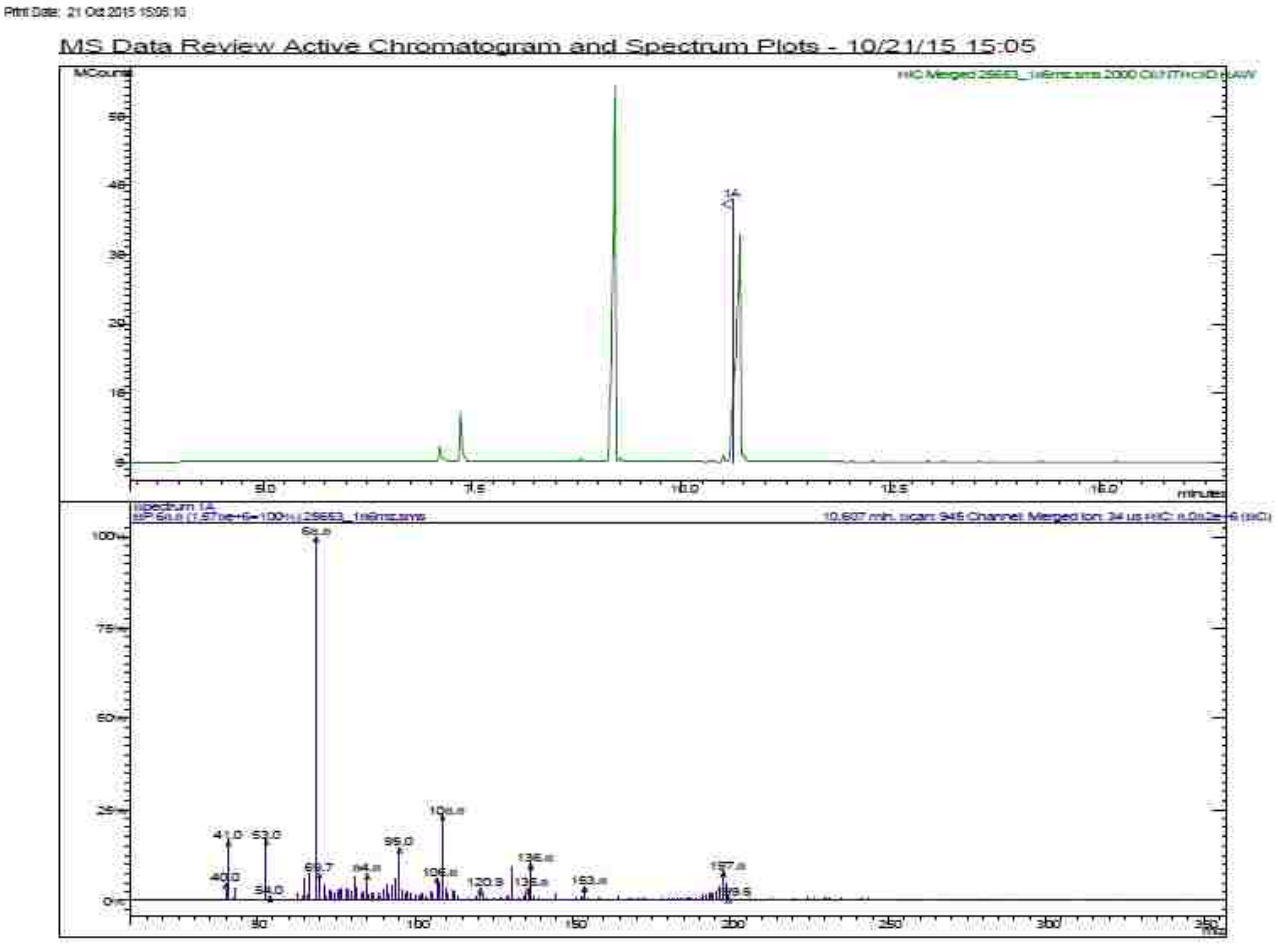
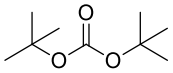


Figure 55. GC/MS chromatograph and spectra of tert-butyl pent-4-en-2-yl carbonate contaminant, EI (filament voltage 70 eV)



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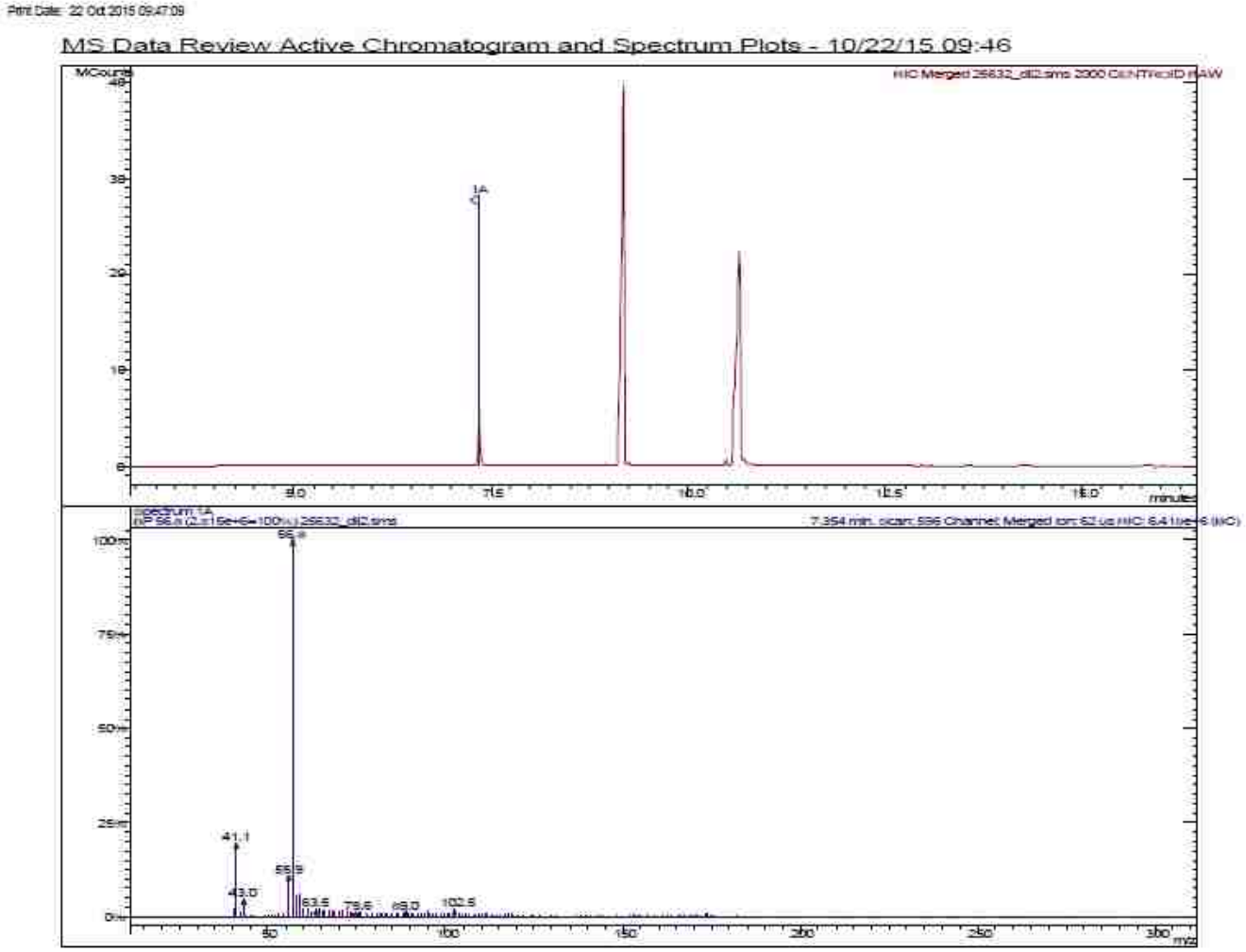
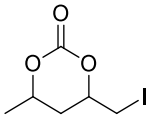


Figure 56. GC/MS chromatograph and spectra of tert-butyl pent-4-en-2-yl carbonate contaminant, EI (filament voltage 70 eV)



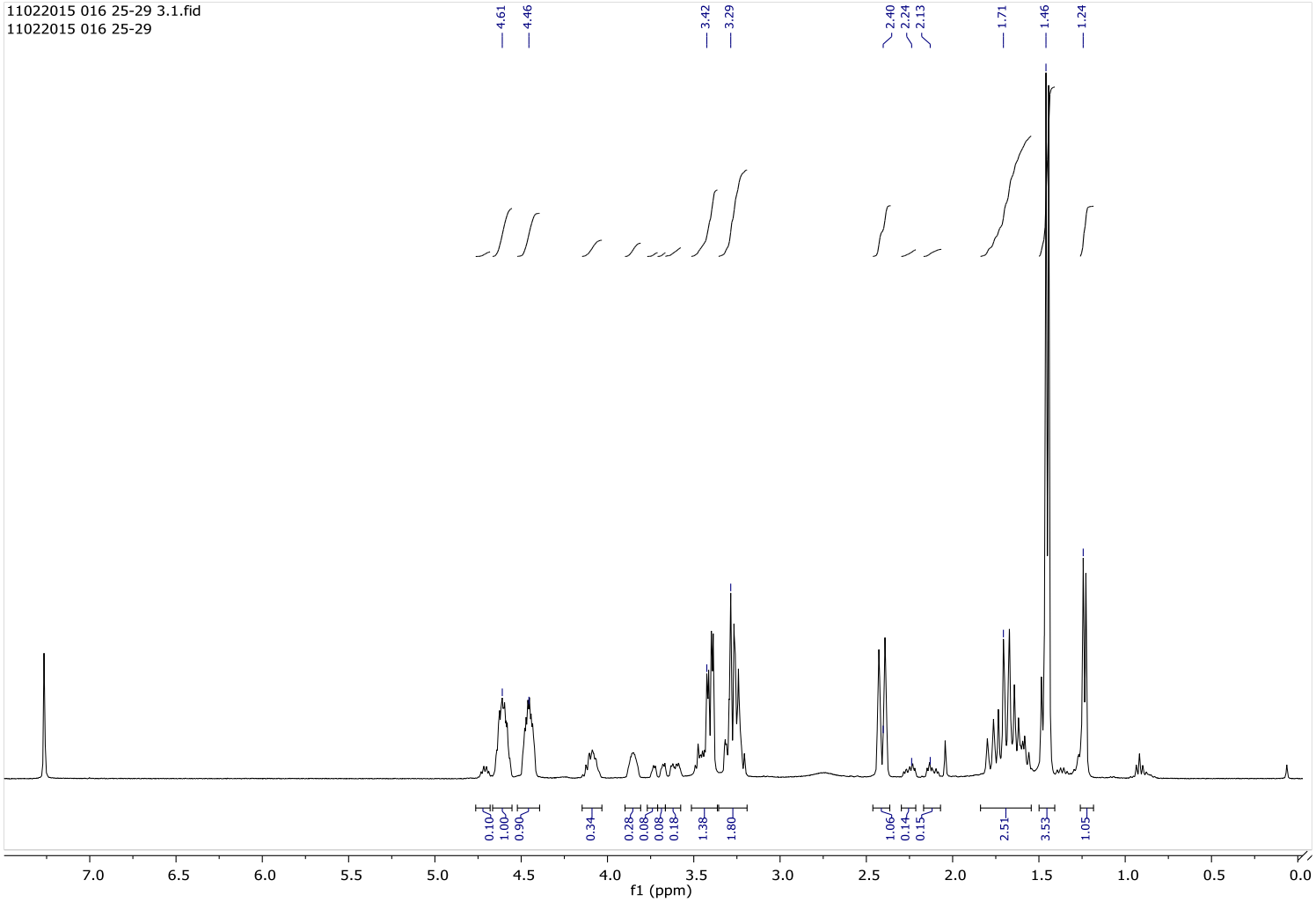


Figure 57. 4-(iodomethyl)-6-methyl-1,3-dioxan-2-one, ^{1}H-NMR (400 MHz, $CDCl_3$)

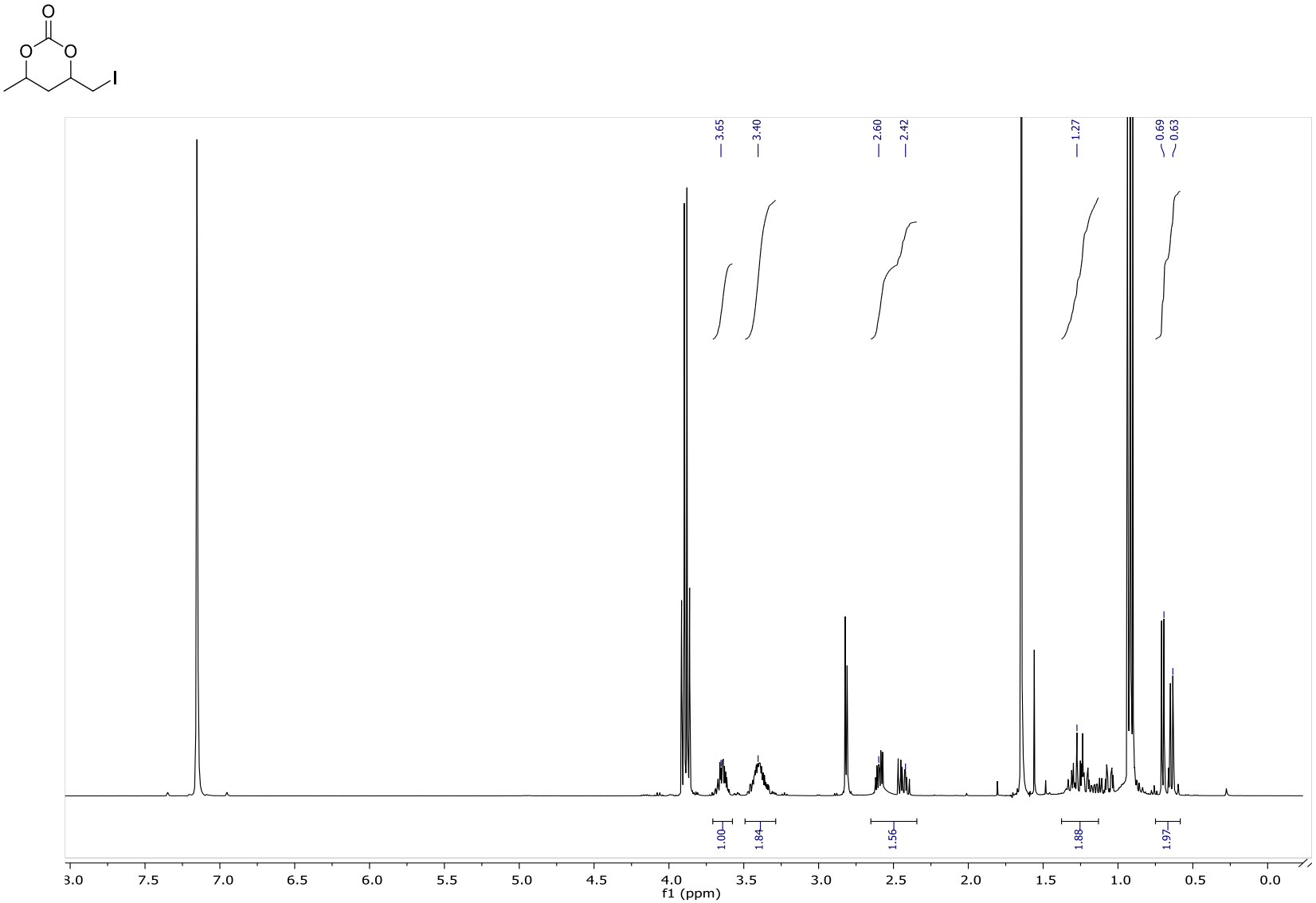
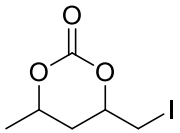


Figure 58. 4-(iodomethyl)-6-methyl-1,3-dioxan-2-one, ^{1}H-NMR (400 MHz, C_6D_6)



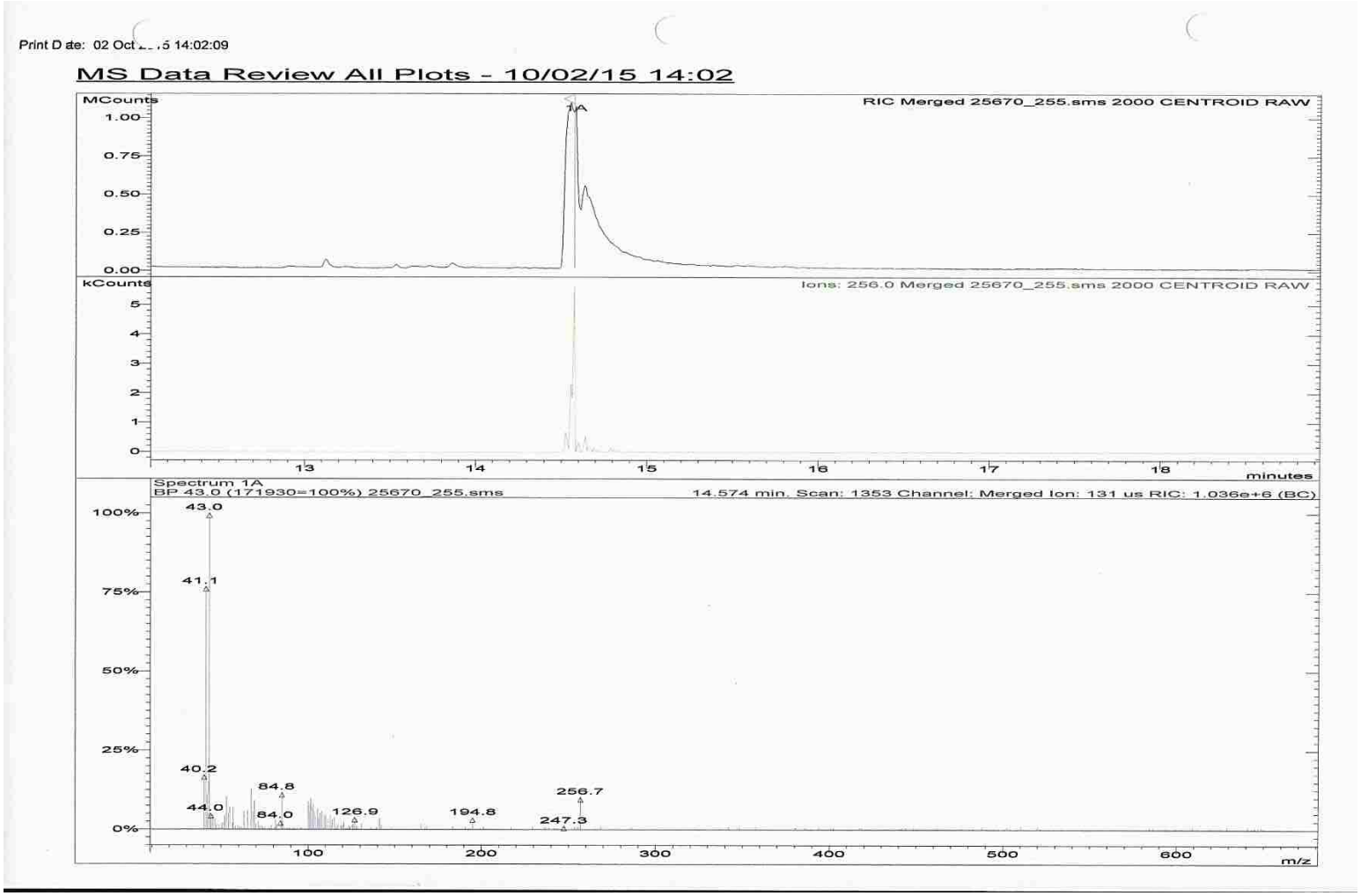


Figure 59. GC/MS of 4-(iodomethyl)-6-methyl-1,3-dioxan-2-one, EI (filament voltage 70 eV)

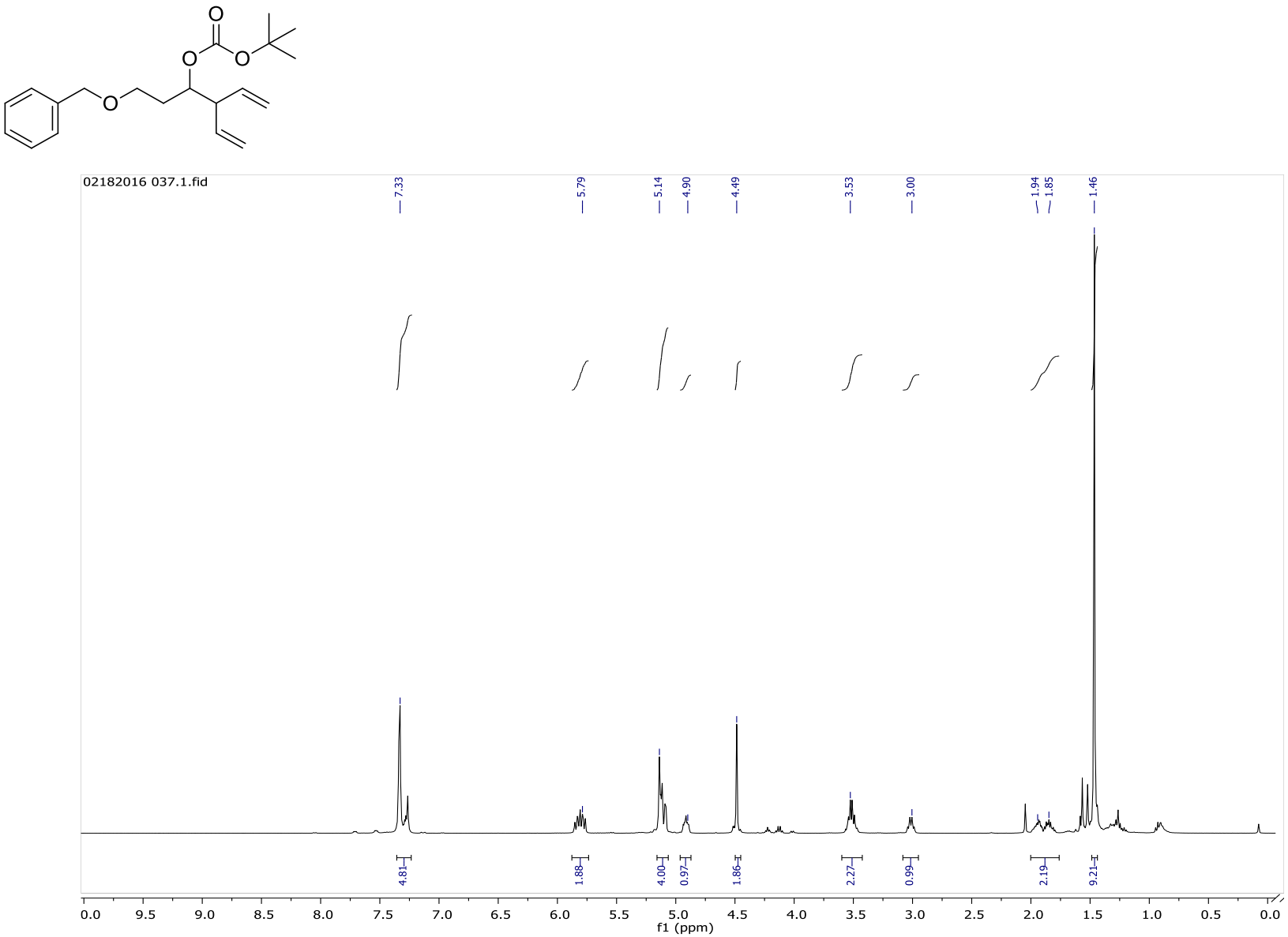


Figure 60. 1-(benzyloxy)-4-vinylhex-5-en-3-yl tert-butyl carbonate, ^{1}H (400 MHz, $CDCl_3$)

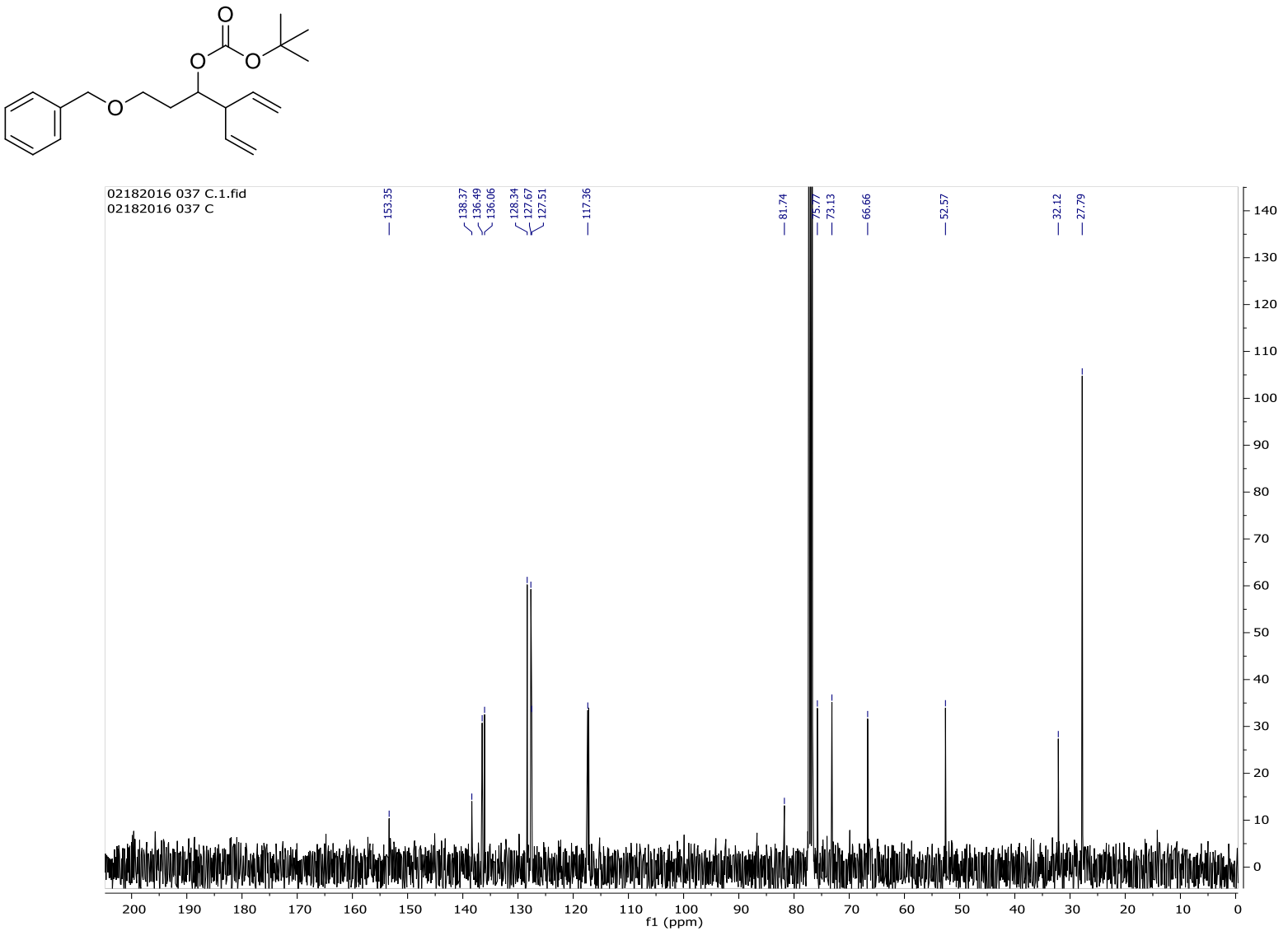


Figure 61. 1-(benzyloxy)-4-vinylhex-5-en-3-yl tert-butyl carbonate, ^{13}C-NMR (101 MHz, $CDCl_3$)

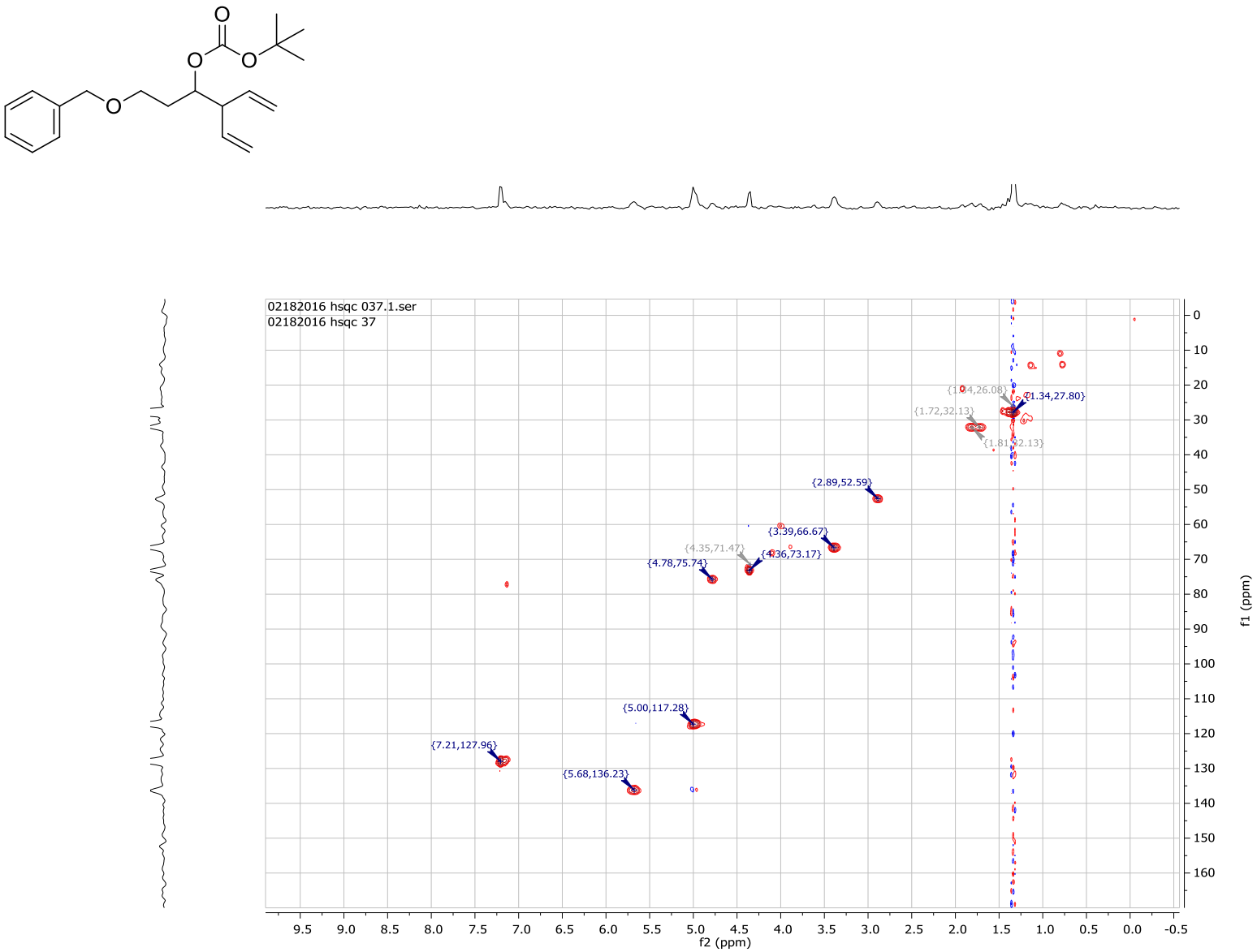


Figure 62. 1-(benzyloxy)-4-vinylhex-5-en-3-yl tert-butyl carbonate, HSQC (400 MHz, $CDCl_3$)

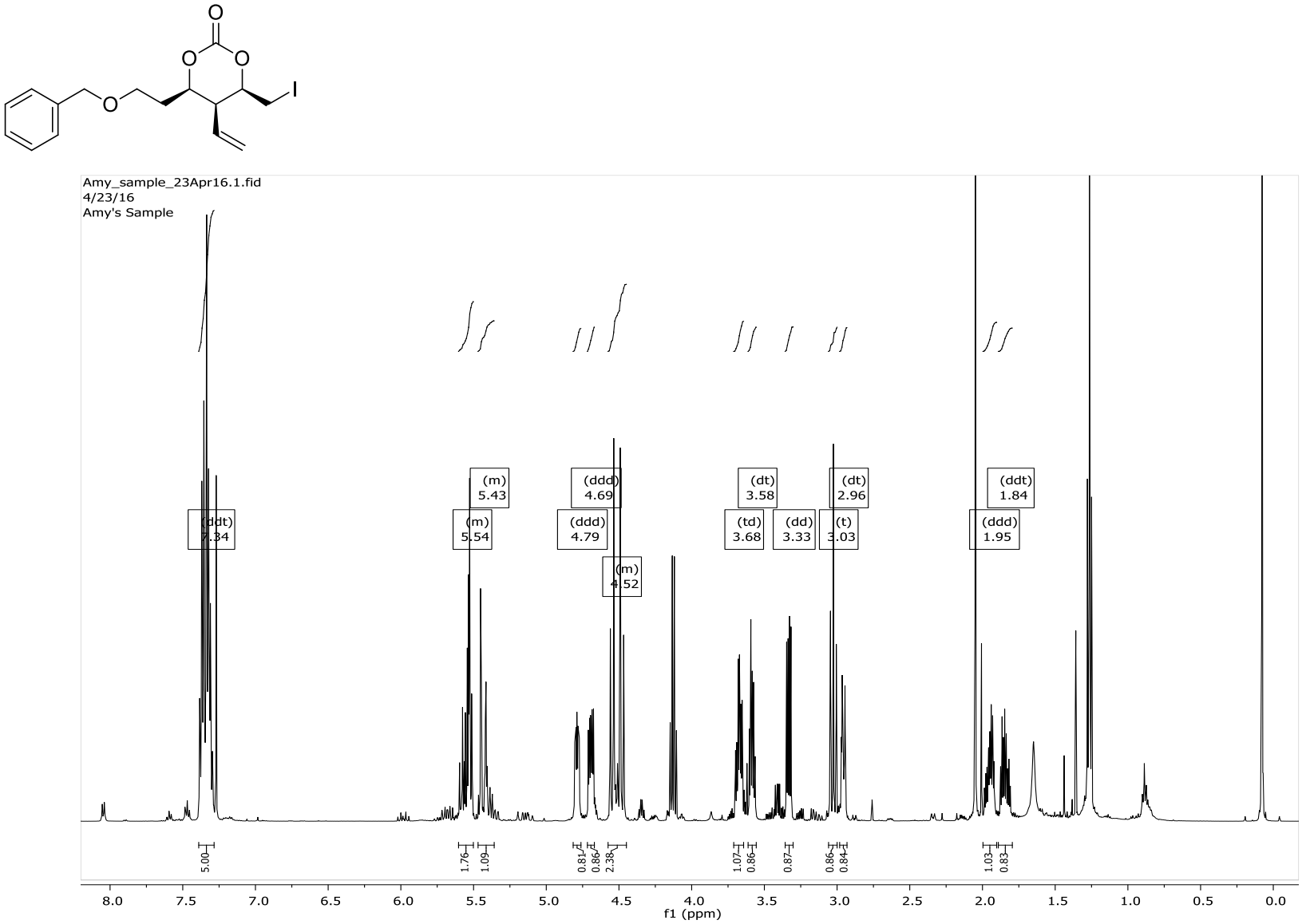


Figure 63. 4-(2-(benzyloxy)ethyl)-6-(iodomethyl)-5-vinyl-1,3-dioxan-2-one, ^{1}H (500 MHz, $CDCl_3$)

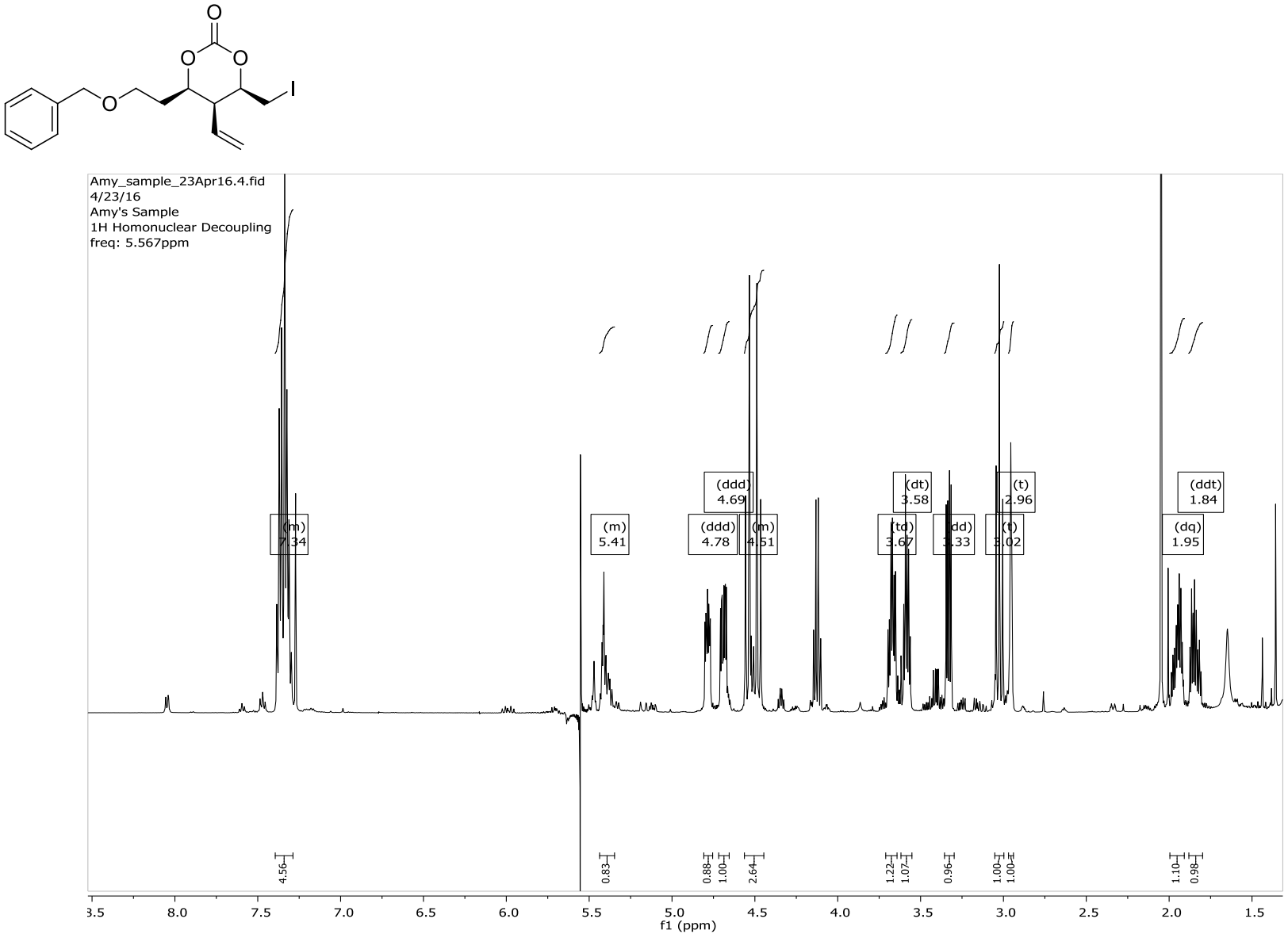
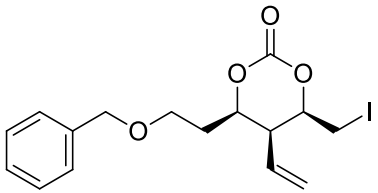


Figure 64. 4-(2-(benzyloxy)ethyl)-6-(iodomethyl)-5-vinyl-1,3-dioxan-2-one, ^{1}H (500 MHz, $CDCl_3$)



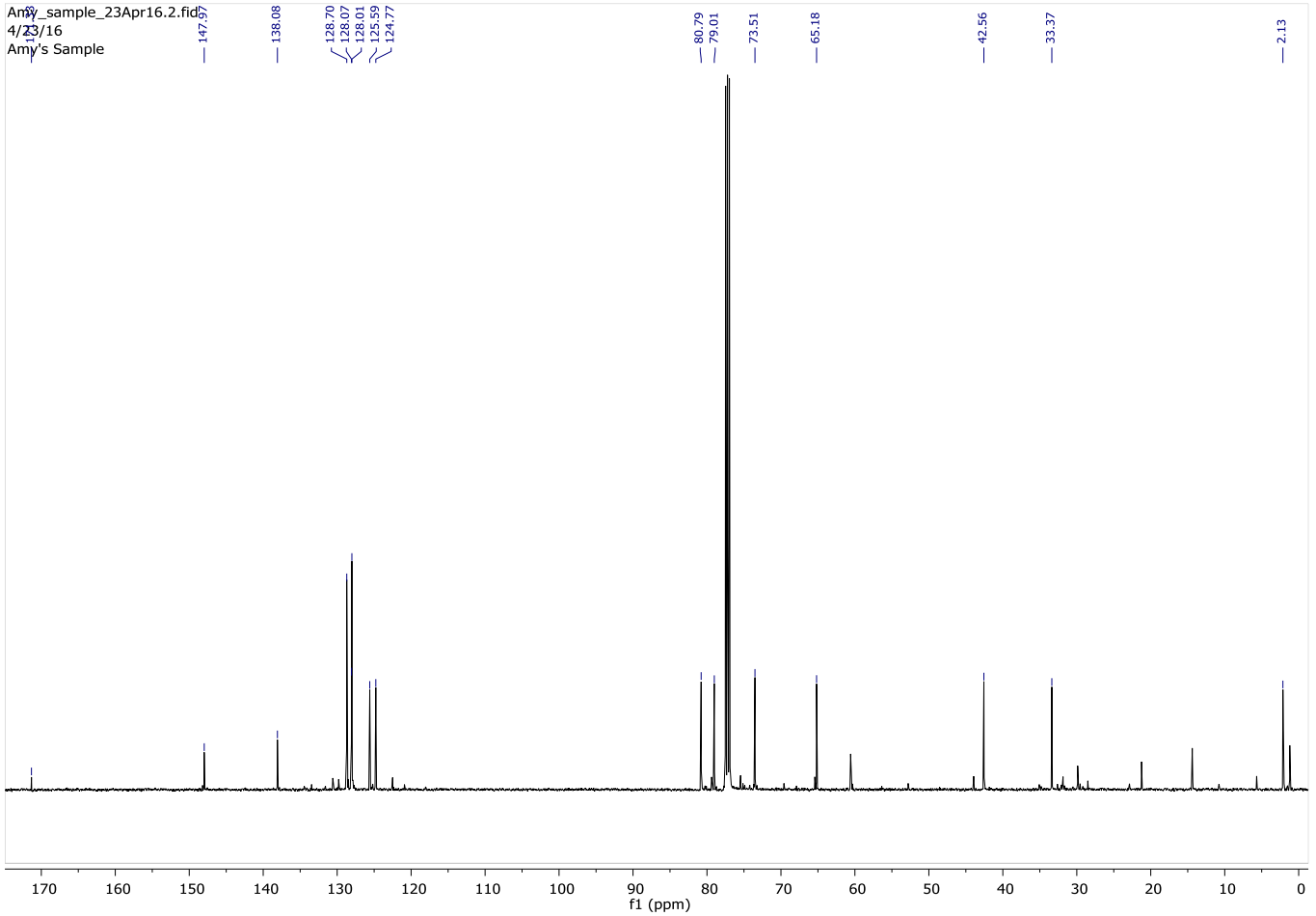


Figure 65. 4-(2-(benzyloxy)ethyl)-6-(iodomethyl)-5-vinyl-1,3-dioxan-2-one, ^{13}C-NMR (126 MHz, $CDCl_3$)

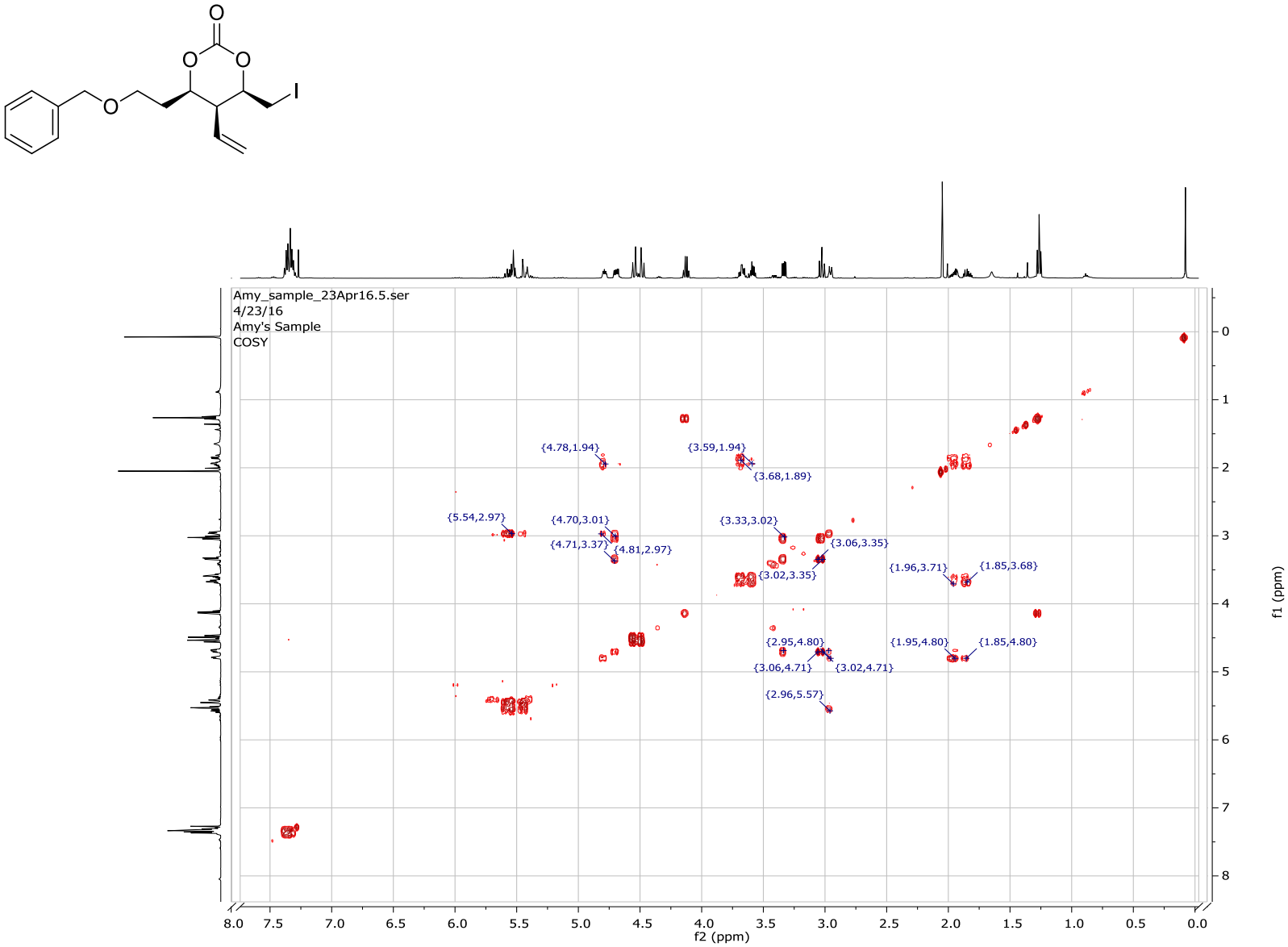


Figure 66. 4-(2-(benzyloxy)ethyl)-6-(iodomethyl)-5-vinyl-1,3-dioxan-2-one, COSY (500 MHz, $CDCl_3$)

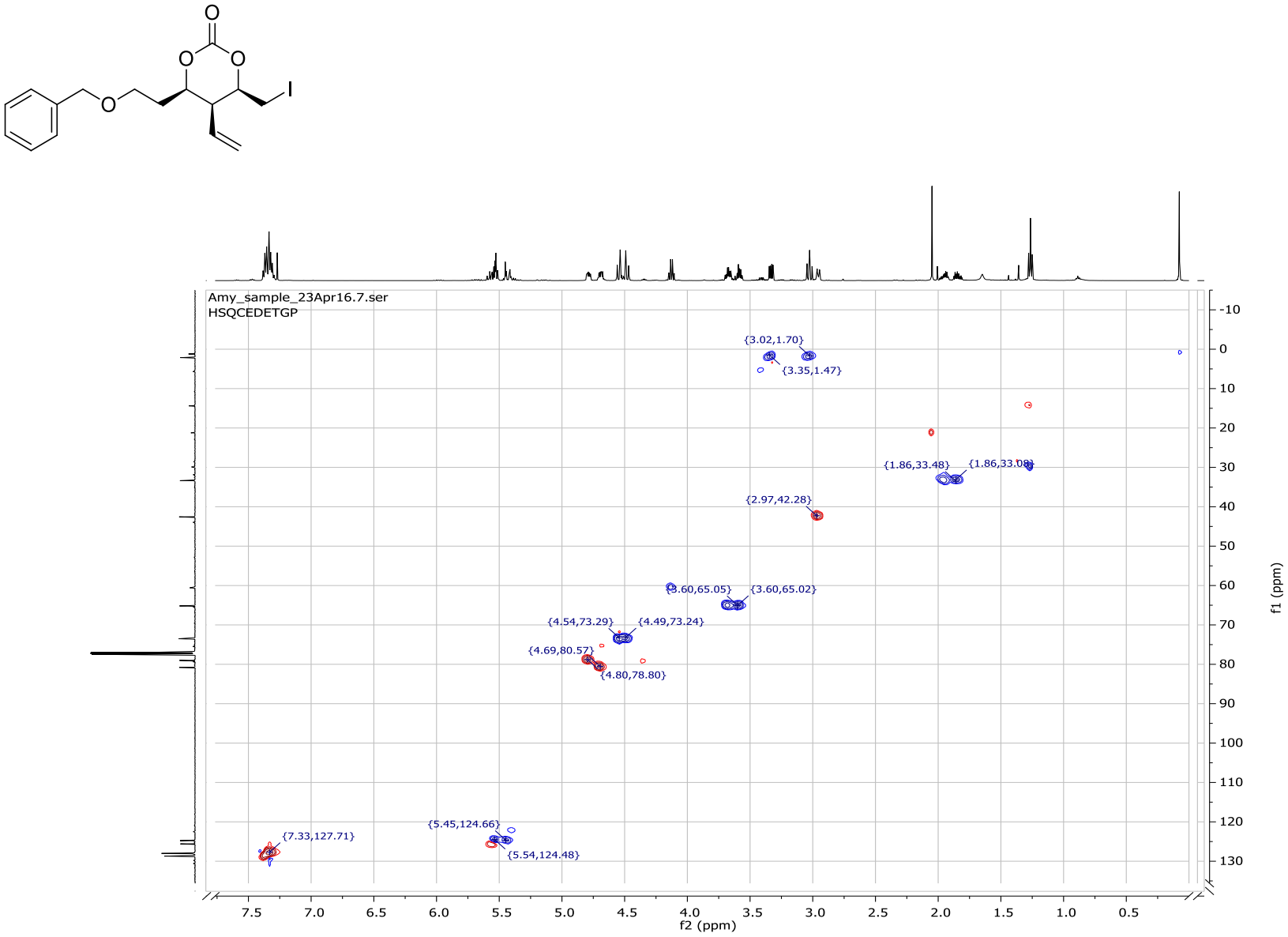


Figure 67. 4-(2-(benzyloxy)ethyl)-6-(iodomethyl)-5-vinyl-1,3-dioxan-2-one, HSQCDEPT (500 MHz, $CDCl_3$)

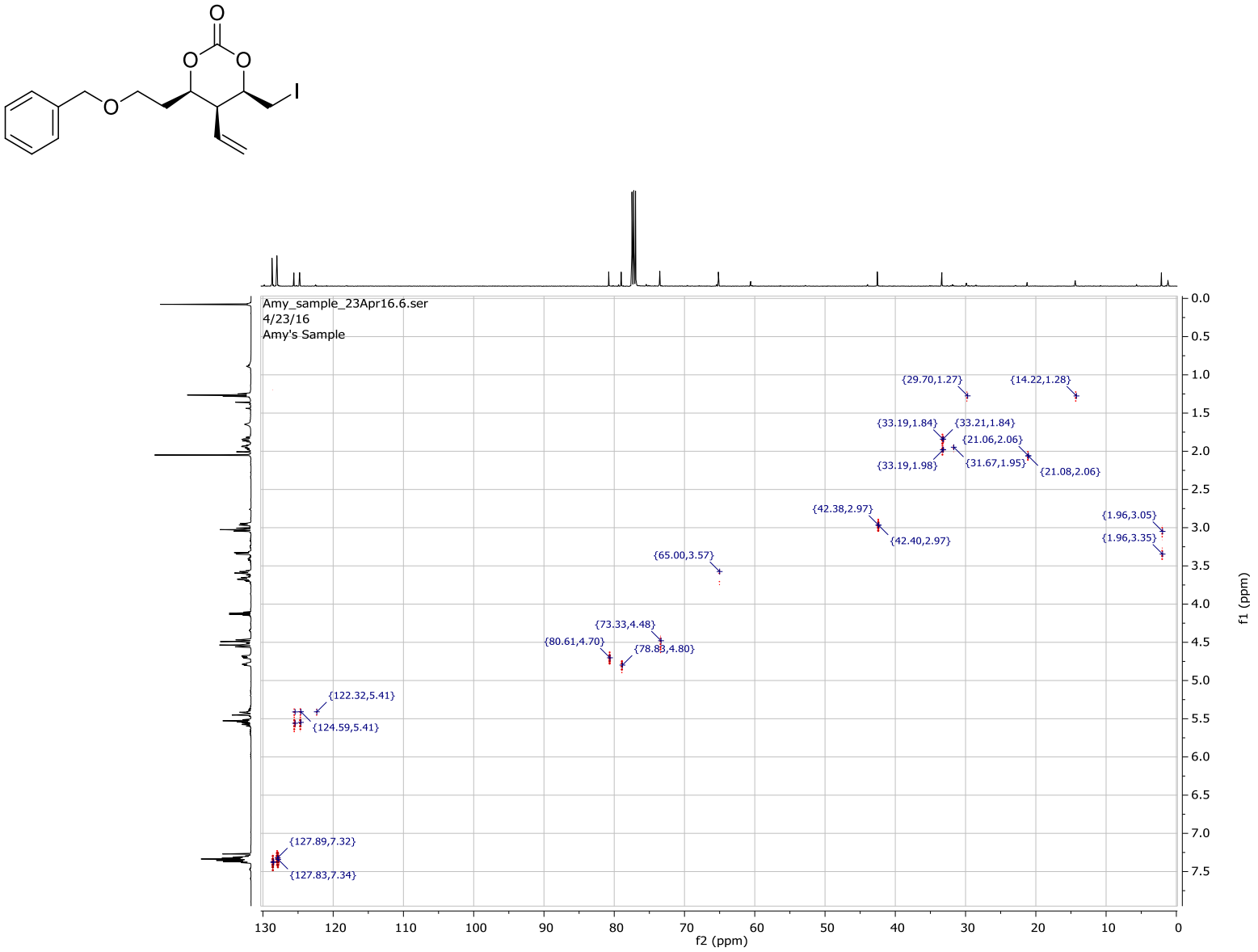


Figure 68. 4-(2-(benzyloxy)ethyl)-6-(iodomethyl)-5-vinyl-1,3-dioxan-2-one, HETCOR (500 MHz, $CDCl_3$)

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VITA

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